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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1952

ORIGINAL ARTICLES

ANALYSIS OF THE AUTOPSY RECORDS OF 157 CASES OF CARCINOMA OF THE PANCREAS WITH PARTICULAR REFERENCE TO THE INCIDENCE OF THROMBOEMBOLISM

By CHARLES M. THOMPSON, M.D.

AND

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PHILADELPHIA, PENNSYLVANIA

CARCINOMA of the pancreas has been well described in several reviews[1,2,3,5,7,10]. As a result rooted concepts concerning symptoms have been replaced with factual information. This has been true especially when autopsy material has been presented. Material derived exclusively from surgical records will show a weighted preponderance of lesions involving the head of the organ. Ingelfinger has stated that, not only are diagnoses made on clinical grounds often erroneous, but palpation or even biopsy at the time of operation may lead to an incorrect diagnosis. Often an accurate diagnosis can be made only at autopsy or by operative procedures that resect large blocks of pancreatic tissue[6].

Analysis of Records. The clinical and autopsy records of 157 cases of carcinoma of the pancreas from January 1, 1936 to September 30, 1947 at the Philadelphia General Hospital were studied (Table 1).

INCIDENCE. In 2 reports including a total of 113 cases of carcinoma of the pancreas there were only 6 patients under the age of 40[4,8]. Three patients in this review were under that age (Table 2). There is an increased incidence of males to females (1.5:1), but the ratio is not as high as had been expected. It can be noted that the number of colored females almost equaled the number of colored males. This lowered the ratio of male preponderance which would be found from analysis of white patients only.

LOCATION OF TUMOR. An autopsy study of carcinoma of the pancreas will show a preponderant number of lesions involving the head of the organ but it will include a large and significant number involving other sites. Almost 21% (33) showed tumor in the body or tail without involvement of the head (Table 3). Almost 70% (110) showed tumor involvement of the head of the pancreas. There was a small number of cases in which the tail alone was the site of the tumor.

SYMPTOMS. None of these symptoms are classified as "early". That symptoms are often first noticed only when a tumor has reached an advanced

TABLE 1.—STATISTICS

Number of Cases	157
Number of Males	94 (59.9%)
White	68
Colored	26
Number of Females	63 (40.1%)
White	38
Colored	25

TABLE 2.—INCIDENCE: AGE, SEX AND RACE

	20–29	*30–39*	*40–49*	*50–59*	*60–69*	*70–79*	*80–89*
White males	1	0	6	19	19	21	2
White females	0	1	3	13	7	13	1
Colored males	0	1	4	9	7	5	0
Colored females	0	0	4	5	10	5	1
Total males	1	1	10	28	26	26	2
Total females	0	1	7	18	17	18	2
Total white	1	1	9	32	26	34	3
Total colored	0	1	8	14	17	10	1

TABLE 3.—LOCATION OF TUMOR

	Cases	*%*
Head of Pancreas	107	68.2
Body of Pancreas	14	8.9
"Diffuse"	14	8.9
Body and Tail of Pancreas	10	6.4
Tail of Pancreas	9	5.7
Head and Body of Pancreas	3	1.9

TABLE 4.—FIRST SYMPTOMS

	Cases	*%*
Weight loss	126	80.8
Anorexia	84	53.8
Pain	82	52.6
Weakness	80	51.3
Nausea and vomiting	57	36.5
Constipation	57	36.5
Jaundice	29	18.6
Diarrhea	23	14.7

stage of growth is understandable for an organ so situated as is the pancreas. Even pain may not occur until there is extension along perineural pathways. Weight loss in our series of cases (Table 4) was extremely rapid and occasionally was unattended by any other symptom. Anorexia differed from the easy satiety of some patients with gastric tumor in that there was an absolute rejection of food in most cases. Pain is discussed separately below. Weakness was frequently extreme and often bordered on complete physical collapse. In a third of the cases with prominent nausea and vomiting there was involvement of the stomach and duodenum by contiguous spread or metastases. Three patients had hematemesis. One showed invasion of the gastric mucosa, another of the duodenum, and a third showed splenic vein obstruction. Constipation occurred twice as often as diarrhea. Fatty stools were reported infrequently.

PHYSICAL FINDINGS. It is reasonable to assume that most patients reaching a city hospital have had symptoms for a longer time than the average patients in other types of hospitals. Physical findings as a result are often those of advanced disease. There were reasons for hepatomegaly other than hepatic metastases which occurred in 67% (116) of the cases. These included hydrohepatosis and biliary stasis. Biliary cirrhosis without evidence of hepatic metastases occurred in less than 10% of the cases. The high incidence of ascites (Table 5) correlated well with the high number of cases with omental, mesenteric and peritoneal metastases. Almost always a palpable epigastric mass was tender. Although 44% of the cases showed an enlarged gallbladder at autopsy, in less than half this number was this organ palpable ante-mortem. However, the Courvoisier principle was not discredited. In 89 cases with jaundice the gallbladder was enlarged at autopsy in 78%.

TABLE 5.—PHYSICAL FINDINGS ON ADMISSION

	Cases	*%*
Palpable liver	103	65.6
Jaundice	88	56.1
Ascites	42	26.8
Epigastric mass	39	24.8
Epigastric tenderness	37	23.6
Palpable gallbladder	29	18.5
Peripheral edema	29	18.5
Glands on rectal shelf	12	7.6
Left supra-clavicular node	9	5.7

ROENTGENOGRAMS. Gastric defects as noted were more common than defects of the duodenum. The "inverted three" sign was reported in only 4 cases. In about one-half of the cases in which a barium enema was done because of constipation or obstructive symptoms, a defect was reported in the transverse colon. Eight cases with skeletal pain had a bone survey and in 7 there was evidence of a spinal destructive lesion (Table 6). This correlated perfectly with evidence of metastasis at autopsy.

TABLE 6.—ROENTGEN-RAY FINDINGS

	Number Cases	*Positive*	
		Cases	*%*
Upper G. I. series	62	48	77.4
Flat plate of abdomen	20	1	5.0
Barium enema	16	7	43.7
Bone	8	7	87.5
G. I. series	62		
Defect of stomach contour		27	43.5
Defect of duodenum		19	30.6
Defect of distal small bowel		2	3.2

TABLE 7.—ANALYSIS OF PAIN

	Cases	*%*
Present at some time	123	78.3
Absent at all times	34	21.7
Character of Pain		
Mild or moderate	89	73.0
Severe	46	27.0
Colic-like	17	13.9
Severe paroxysms without colic	12	9.0
Time of Appearance		
Early in course	82	67.2
Late in course	35	28.7
Not stated	5	4.1

Location of Pain

	With Back Pain	*Without Back Pain*	*Totals*
Upper abdomen not classified	8	9	17
Epigastrium	10	17	27
Right upper quadrant	7	14	21
Left upper quadrant	3	2	5
Peri-umbilical	0	4	4
Lower abdomen	2	4	6
Abdomen (unclassified)	5	19	24
Lower left chest	1	2	3
Pain in back only			9
Miscellaneous (not classified)			6

TABLE 8.—ANALYSIS OF LABORATORY FINDINGS

		Cases	%
Anemia (below 3.9 million R.B.C. or 11.5 gm. HBG)		75	47.7
Average R.B.C.	3.27 million		
Average hemoglobin	9.78 gm.		
Glycosuria (114 cases)		25	17.4
Fasting blood sugar (144 cases)			
Normal		107	74.3
120–149		16	11.1
150 or above		21	14.6
Glucose tolerance test (6 cases)			
Decreased		3	50.0
Increased		1	17.7
Normal		2	33.3
Serum amylase (9 cases)			
Normal		7	77.8
Elevated		2	22.2
Serum lipase (14 cases)			
Normal		6	42.9
Elevated		8	57.1
1.2	1		
1.4	1		
1.8	1		
2.0	1		
2.2	2		
3.2	1		
4.2	1		
Serum bilirubin (T) or icterus index (83 cases)			
Elevated		73	87.9
Fluctuating early		9	12.3
Alkaline phosphatase (26 cases)			
Elevated		22	84.6
With jaundice		21	
Without jaundice		1	
Normal			
With jaundice		2	
Without jaundice		2	
Total Cholesterol (64 cases)			
Increased			
With jaundice		34	
Without jaundice		3	
Normal or decreased			
With jaundice		19	
Without jaundice		8	
Cholesterol esters (60 cases)			
Decreased		52	
With jaundice		48	
Without jaundice		4	
Normal		8	
With jaundice		3	
Without jaundice		5	

Analysis of Pain. Only about a fifth of the patients escaped pain from onset of symptoms to death (Table 7). In 70 cases pain was present in the upper abdomen and in 28 of these there was associated back pain aggravated by recumbency. Frequently the pain was periumbilical or lower abdominal in location. Some complained of diffuse, poorly localized abdominal pain. Nine patients had back pain only. Considering the occasional reference of pain in acute pancreatitis to the lower chest, there is a low incidence of chest reference in our series. The incidence of paroxysmal pain provides an explanation for the confusion with cholecystitis or cholelithiasis which existed in some instances. When pain was classified as late, the average time for its appearance was 6 months after the onset of another first symptom.

It is pertinent to observe that there was a lower incidence of jaundice than there was of pain. By comparison, only 56.7% (89) had jaundice at some time during the course. Only 24.7% (22) had painless jaundice at all times. Only 7% (11) had neither pain nor jaundice before death.

Laboratory Findings. Only significant laboratory findings that were available on the records are presented (Table 8). The number of cases with reducing substances in the urine could be anticipated in a series which included many with extensive pancreatic destruction. It is more difficult to evaluate instances of elevated blood sugar or impaired glucose tolerance. Factors affecting glucose tolerance such as age and inanition before tests could not be separated from factors depending on islet cell integrity or hepatic storage of glycogen. Slightly more than 12% of those with bilirubinemia showed inconstant or variable levels by laboratory standards. Serum enzyme determinations without provocative stimulation were done in relatively few of the cases. The serum lipase appeared to be a more reliable index. Only 1 case without jaundice showed an elevation of the alkaline phosphatase determination. The test was not done in enough cases without jaundice to check its reliability as an indication of intrahepatic metastases. Thirty-five of the cases with reduced esters showed metastases. This includes 4 cases in which there was no laboratory evidence of jaundice.

Metastases. The widespread nature of metastases from carcinoma of the pancreas is well known. Most series report the highest incidence of metastases by way of the perineural spaces, lymphatics, or blood channels to regional lymph nodes, the liver and the gastrointestinal tract[1,2,5]. At the other extreme is the absence in our series of any case with brain substance metastases, although the dura was involved in one. Metastases to serous membranes were associated with a high incidence of effusions. Peritoneal metastases had associated ascites in 100%; pleural metastases had effusion in 50%; mesenteric had ascites in slightly more than 73%, and pericardial metastases had an associated pericardial effusion in 75% of cases. More effusions were reported at autopsy than could be accounted for by cavity metastases.

Thromboembolism. A higher incidence of arterial thromboses than of venous thromboses is contrary to what would be expected in final neoplastic disease. Almost half of these are the result of aortic and pulmonary arterial thromboses. A large number of venous thromboses were in the portal system. Except for 8 cases with pulmonary artery embolism, all the infarctions were the result of arterial and venous thromboses. If cases in which the tumor is described as diffuse are ex-

TABLE 9.—LOCATION OF METASTASES

	Cases	*%*
Liver	106	67.5
Regional lymph nodes	103	65.6
Gastrointestinal tract	58	67.5
Esophagus	2	
Stomach	8	
Duodenum	20	
Small intestine	14	
Colon	11	
Rectum	3	
Lungs	37	23.6
Adrenals	30	19.1
Peritoneum	25	16.0
Kidneys	20	12.7
Omentum	16	10.3
Pleura	16	10.3
Mesentery	15	9.6
Bones	14	8.9
Common duct	12	7.7
Spleen	12	7.7
Gallbladder	11	7.1
Diaphragm	8	5.1
Adjacent veins	5	3.1
Cystic duct	4	2.6
Pericardium	4	2.6
Myocardium	3	1.9
Common or hepatic ducts	3	1.9
Skin	3	1.9
Prostate	1	.06
Dura	1	.06
Bone metastases	14	
D 3	1	
D 12	1	
L 1	5	
L 2	5	
L 3	4	
L 4	4	
L 5	2	
Sternum	4	
Left 3rd rib	2	

TABLE 10.—CLASSIFICATION OF THROMBOEMBOLIC COMPLICATIONS

	Cases	*%*
Arterial embolism	8	
Pulmonary	8	100.0
Arterial thrombosis	26	
Aortic (Mural)	7	26.9
Pulmonary	5	19.2
Cerebral	3	11.5
Renal	3	11.5
Iliac	3	11.5
Cardiac (Mural)	2	7.7
Mesenteric	1	3.8
Splenic	1	3.8
Coronary	1	3.8
Venous thrombosis	21	
Portal	5	23.8
Splenic	5	23.8
Pancreatic	2	9.5
Inferior vena cava	2	9.5
Common iliac	2	9.5
Superior mesenteric	1	4.8
Inferior mesenteric	1	4.8
Adrenal	1	4.8
Ovarian	1	4.8
Cervical	1	4.8
Infarctions	40	
Splenic	12	30.0
Myocardial	10	25.0
Pulmonary	8	20.0
Renal	7	17.5
Hepatic	3	7.5
Total cases with thrombo-embolism	48	30.8
Single	25	52.1
Multiple	23	47.9

TABLE 11.—LOCATION OF TUMOR WITH SINGLE OR MULTIPLE THROMBOEMBOLISM

				% Multiple
Head				
Single	18	Multiple	12	40.0
Head and Body				
Single	0	Multiple	1	100.0
Body				
Single	0	Multiple	3	100.0
Body and Tail				
Single	2	Multiple	4	66.6
Tail				
Single	2	Multiple	3	60.0
Diffuse				
Single	3	Multiple	0	0

cluded, there is a predominance of multiple vascular complications in cases in which the body and tail of the pancreas are involved.

Discussion. Sproul's findings on the number of venous and arterial thromboses in carcinoma of the pancreas have been reported[11]. In over 4000 consecutive autopsies venous thromboses were found 332 times and carcinoma of various sites of origin was present in about one-half of these. Arterial thromboses occurred 153 times. Only a minor number of these were associated with carcinoma. However, in Sproul's report carcinoma was a major finding in cases with pulmonary arterial thromboses.

This investigator went on to analyze the incidence of thromboses in carcinoma of various organs. There was a high incidence of thrombosis in carcinoma involving any part of the pancreas. This was only slightly higher than the incidence when the primary site was in such organs as the kidney or liver. However, the incidence of multiple thromboses was much greater in carcinoma of the pancreas. This was particularly true when the body or tail of the pancreas was involved. Then the incidence rose to a fraction more than 31% and could be compared with an incidence of slightly more than 1% of multiple thromboses in carcinoma of the stomach. Furthermore, he reported that, although about 13% showed single thrombosis when there was secondary malignancy involving the pancreas, none of these 83 patients had multiple thromboses. Thus the issue is not the incidence of single thromboembolism but the number of cases showing multiple vascular abnormalities. This particularly holds for tumor of the body and tail of the pancreas.

The finding of thromboembolism in a patient with an obscure illness raises the suspicion of malignancy. In this record, the discovery or the assumed significance of visceral thromboembolism was not noted. Presumably many were missed before death and when discovered the diagnosis of visceral neoplasm was not frequently suggested by their presence. Although theoretical grounds for the increased incidence of thromboembolism in malignancy and particularly that involving the pancreas have been proposed, no indisputable basis has been discovered. It has been suggested that in carcinoma of the pancreas there is an accelerating effect on blood coagulation.

Recently, Moolten *et al.* suggested that the role of blood platelets in increasing the tendency to thromboembolism in malignancy is a predominant one[9]. The total platelet count was less important than increased platelet adhesiveness. They stated that the detection of increased platelet adhesiveness might prove helpful in the diagnosis of suspected malignancy. Thrombocytosin, which increases platelet adhesiveness, is a by-product of necrosis within a tumor. In carcinoma of the pancreas this enzymatic accelerator, along with increased levels of pancreatic lipase, may result in the development of increased platelet adhesiveness and "endothelial wetability". Carcinoma of the body or tail of the pancreas may be associated with increased thromboembolic phenomena (multiple thromboses) because the appearance of other first symptoms such as might result from ductal or pyloro-duodenal obstruction lags during the growth of the tumor. The morbid process is at least superficially slowed and thromboembolism may be an original or the most evident manifestation.

Summary. The records of 157 cases of carcinoma of the pancreas have

been reviewed. All records were studied from the time of admission to the hospital until autopsy. Some features of the clinical findings are presented. These emphasize the value of correlating clinical and autopsy material. A high incidence of thromboembolism is reported. The frequency of vascular phenomena in carcinoma of the pancreas deserves re-emphasis. It may, by reflection, aid in the solution of some grave diagnostic problems. The potential role of platelet adhesiveness is discussed and reference is made to the works of others.

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ADDISON'S DISEASE IN THE NEGRO*

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Addison's disease was formerly considered to be of rare occurrence in the Negro race[4]. Lisa, Solomon, and Gordon[7] reviewed the literature in 1942 and could find only 17 cases, to which they added 3. Subsequent reports by Conn and Mathews[2], and by Bergner and Eisenstein[1], have increased the number to 31. Undoubtedly many more cases have been seen and not reported. Most of the recent authors[1, 2, 7] have suggested that the disease is much more common in Negroes than has been supposed. Conn and Mathews[2] discussed various reasons for the paucity of published reports. It is generally agreed that difficulty in recognizing pigmentary changes in the Negro causes many cases of Addison's disease to go unrecognized.

We have recently seen several Negro patients with Addison's disease, who presented very striking pigmentary changes. This led us to review the cases of Addison's disease seen at the Medical College of Virginia Hospital over the past 10 years. Five cases were found in Negroes admitted to St. Philip and Dooley Hospitals over this period, 4 recognized clinically and 1 diagnosed at autopsy. One additional case has been seen at the Richmond, Virginia, Veterans Administration Hospital. These 6 cases constitute the subject of this report.

Case Reports. Case 1. H. L., a 34-year-old Negress, was admitted to St. Philip Hospital on August 28, 1941. She had noticed progressive weakness for 6 months, with weight loss from 230 to 180 pounds. During the past 8 months her skin color had changed from brown to deep black. She had been anorexic for 6 weeks and had been vomiting for 2 days.

Examination showed a jet black Negress (Fig. 1), still obese but weak. The palms showed increased pigmentation along the skin creases. The lips, oral mucosa, and tongue showed patches of bluish-black pigment. The heart sounds were very faint. Blood pressure varied from 85/55 to 110/70. The lungs were clear.

Laboratory studies included: urinalysis negative; blood counts initially normal, but after hydration hemoglobin 9.6 gm. and red cells 3,400,000; non-protein nitrogen 40 mg. per 100 cc.; fasting blood sugars from 73 mg. to 94 mg.; serum chloride 94 mEq/L; CO_2 combining power 36 vol. per cent. Chest Roentgen films showed the lungs clear and the heart small. An intravenous pyelogram was normal. A glucose tolerance test showed a moderately flat curve with no fall below 80 mg. in 5 hours. Skin biopsy from the left thigh showed intense melanin pigmentation of the epidermis, most marked in the basal cell layer. This was indistinguishable from normal Negro skin except for the unusual amount of pigment.

* This paper was presented in abstract before the American Clinical and Climatological Association, November 5, 1951.

On the second day of a salt deprivation test, the patient became extremely weak and drowsy, vomited, and her blood pressure fell to 70/45. This was considered diagnostic of Addison's disease, and the test was terminated. The patient was treated intensively with glucose in saline solution and DOCA, with gradual improvement. Over the next month she was regulated with decreasing doses of DOCA, with a daily supplement of 20 gm. of salt. Weight was stable and blood pressure 110/70 when she was discharged on October 14, 1941.

She was followed in the Out-Patient Clinic for 5 months. The salt supplement was reduced to 10 gm. daily, and DOCA, 5 mg., was given once a week. She maintained her weight and blood pressure remained around 110/70. She felt stronger but was still unable to work. She was last seen in March, 1942. It was subsequently learned that she had moved to another city where she died 2 years later.

Case 2. M. L. D., a 2½-year-old Negro female infant, was admitted to Dooley Hospital on November 8, 1948, with convulsions which had begun that day. She had been previously treated at the age of 1 month for severe enteritis, dehydration, shock, and septicemia, with recovery. She had apparently been well from that time to the day of admission. Examination showed high fever and evidence of otitis media. No abnormal skin pigmentation was noted. In spite of treatment with penicillin and fluids she lapsed into deep shock and died 30 hours after admission. Autopsy showed most of both adrenal glands to have been replaced by fibrosis, calcification, and heteroplastic bone formation. This was believed to have resulted from the septicemia at the age of 1 month. This case has been reported in detail by White and Sutton[9].

Case 3. J. H., a 43-year-old Negro male janitor, was admitted to St. Philip Hospital on February 22, 1951, in a confused, lethargic state. He later stated that he had been treated for "low blood pressure" for about a year. He had been stoking a hot furnace and had recently become weak and sick. He stated that his skin had turned very dark 2 years before, which he attributed to "someone poisoning me."

Temperature was 102.4°, pulse 108, and blood pressure 88/74. The patient was drowsy and weak and talked incoherently. The skin was very dark, being almost black on the face and forearms (Fig. 2). The palmar creases were deeply pigmented. Patches of bluish-black pigment were present on the buccal mucosa, gums, palate, and dorsum of the tongue. Dehydration was marked. There was no hair on the trunk, and axillary hair was sparse. The testes were softer than normal. A penile scar was present.

Fig. 1.—Patient H.L. (Case 1) is on the left. The patient on the right was selected from the ward by Patient H.L. as having skin color most closely approximating hers before she turned dark.

Initial laboratory data included: urinalysis negative; blood counts not remarkable except for 5% eosinophils on differential, with an absolute eosinophil count of 225 per c.mm.; blood sugar 102 mg. per 100 cc.; non-protein nitrogen 54 mg.; serum sodium 132 mEq/L, potassium 5.4 mEq/L, chloride 100 mEq/L, and CO_2 combining power 65 vol. per cent; blood Wassermann positive in 1:16 titer. Spinal fluid was clear, with 14 lymphocytes,

total protein 128 mg., and Wassermann positive in 0.3 cc. dilution.

The patient was thought to be in Addisonian crisis, and also to have syphilis of the central nervous system. He was treated with glucose in saline solution, aqueous adrenal extract, and DOCA. He was also given penicillin, which was continued for 6 weeks, a total of 15 million units being given. Within 24 hours the blood pressure was normal, and the patient was afebrile and ambulatory, although still confused. Adrenal extract and DOCA were stopped, and further studies of adrenal function were begun. A water excretion test[8] was strongly positive. Urinary 17-ketosteroids were 1.7 mg./24 hr. Urinary corticosteroids* were 0.09 mg./24 hr. Eosinophils fell only 32%, 4 hours after ACTH, 25 mg. Insulin tolerance test, 0.05 unit of insulin/kg. body weight being given intravenously, showed fall in blood sugar from 88 mg. to 40 mg. per 100 cc. in 30 minutes, with rise to only 70 mg. in 2 hours. Chest roentgenograms showed old pleural adhesions. Abdominal films showed no calcification of the adrenals. Skull roentgenogram was normal. Tuberculin skin test (O.T. 1:10,000) was positive.

The patient's mental status gradually improved. Three grams of extra salt daily were given, and regulation with intramuscular DOCA was begun. With DOCA 2 mg. daily, blood pressure remained around 110/70, weight was constant, and no edema was noted. On April 3, six 75-mg. DOCA pellets were implanted. The patient was discharged to be followed in the Out-Patient Clinic.

On April 14, 1951, he returned with fever of 102° and cough. There were fine basal rales, distended neck veins, and some ankle edema. Blood pressure was 130/80. Eosinophil count was 165 per c.mm. Serum electrolytes were normal. Chest roentgenogram showed pulmonary congestion. He was given cortisone 200 mg. in 1 day, then 100 mg. daily for 2 more days. He was also given penicillin and a mercurial diuretic. Fever subsided and did not recur. Good diuresis occurred, and pulmonary congestion and ankle edema disappeared. In a week he was feeling very well and was discharged with instructions to omit extra salt.

Edema recurred and blood pressure rose to 150/100. On April 30, 3 of the implanted DOCA pellets were removed. Edema and hypertension of 160/100 persisted, and on

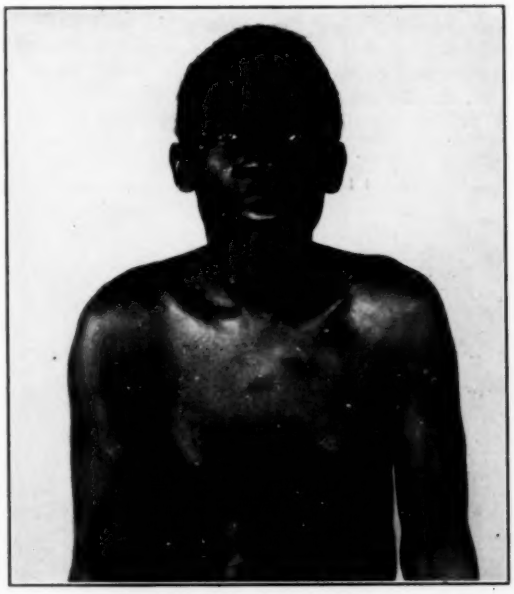

FIG. 2.—Patient J.H. (Case 3).

* Urinary formaldehydogenic corticosteroids were determined by a method similar to that of Corcoran and Page[9]. The normal range in this laboratory is 0.3 to 1.0 mg./24 hr.

June 20, two of the 3 remaining pellets were removed.

On June 25 the patient was brought to the hospital in hypoglycemic coma. Blood sugar was 46 mg. and he responded promptly to intravenous glucose. He again showed ankle edema and hypertension of 160/100. Adrenal extract was given for 24 hours. He was placed on a low salt intake with frequent feedings. Edema subsided but blood pressure remained around 140/100. He felt well but fasting blood sugars were reported from 40 to 66 mg. Urinary corticosteroids at this time were 0.07 mg./24 hr., and 17-ketosteroids 1.6 mg./24 hr. It was apparent that the patient had severe deficiency of the carbohydrate regulating adrenocortical factor. Oral cortisone was begun, at first 25 mg. daily, later 12.5 mg. daily. No further hypoglycemia occurred. Also blood pressure gradually declined to 110/80, and no further edema developed. Because of the apparent increase in severity of his Addison's disease, it was suspected that he might have progressive tuberculous destruction of the adrenals. A course of streptomycin and para-aminosalicylic acid was given. Pyelogram showed irregular filling of the lower calyces of the right kidney, but definite proof of a tuberculous process was not obtained. He was discharged on July 21, feeling very well, to continue oral cortisone 6.25 mg. twice daily and to have further studies for possible renal tuberculosis in the clinic.

The patient failed to keep his clinic appointment and ran out of cortisone. Without cortisone he felt weak and dizzy but got into no serious difficulties. Blood pressure remained 115/85. He has been subsequently seen and put back on cortisone.

Case 4. A. G., 39-year old Negro male, was admitted to St. Philip Hospital on June 3, 1951. He had been treated 2 years before for tuberculous osteochondritis of the right second rib. He had not come to the clinic as directed and had not been seen since. During the past year he had been very weak and had lost much weight. In the past 2 weeks he had become very short of breath. A cousin stated that his skin had turned much darker during the past year.

Examination showed a very ill, emaciated, lethargic Negro whose skin was dry and extremely dark (Fig. 3). The lips were deeply pigmented, and patches of pigment were present on the gums and buccal mucosa. Temperature was 99.4°, blood pressure 70/40. The chest showed signs of left pleural effusion. Heart sounds were distant. There was no hair on the trunk, and axillary and pubic hair was scanty.

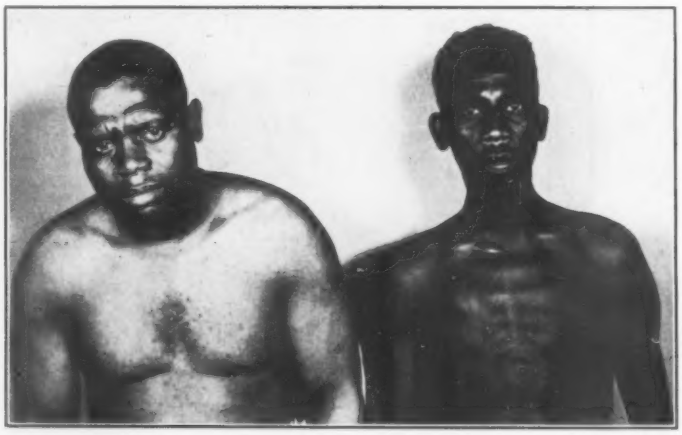

Fig. 3.—Patient A.G. (Case 4) is on the right. The patient on the left was selected by Patient A.G. as most closely approximating his former skin color.

Laboratory studies included: urinalysis negative; hemoglobin 9.0 gm.; erythrocytes 3,960,000; leukocytes 7750, with normal differential count, and an absolute eosinophil count of 457 per c.mm.; serum sodium 116 mEq/L, potassium 5 mEq/L, chloride 92 mEq/L, and CO_2 combining power 67 vol. per cent non-protein nitrogen 44 mg.; fasting blood sugars, 84 and 60 mg. per 100 cc. Eosinophil count increased by 8% 4 hours after ACTH, 25 mg. Urinary 17-ketosteroids were 1.5 mg./24 hr., and

urinary corticosteroids 0.10 mg./24 hr. Repeated sputum smears and cultures were negative for tubercle bacilli, as was culture of the pleural fluid. Tuberculin skin test was strongly positive. Blood Wassermann was positive in 1:8 titer.

The patient was treated with streptomycin, para-aminosalicylic acid, penicillin, and cortisone 25 mg. daily. Fever, which had previously risen to 102°, promptly subsided, but blood pressure remained around 80/50. DOCA and a daily salt supplement of 3 gm. were added, and blood pressure rose to 100/70. Cortisone was subsequently reduced to 12.5 mg. daily. The patient improved steadily and all signs of pleural fluid disappeared. Subsequent chest films showed the lungs clear. On July 12, cortisone was stopped, DOCA and salt being continued. The patient still felt well. Intramuscular testosterone propionate was given. On July 20, three 75-mg. DOCA pellets and four 75-mg. testosterone pellets were implanted. Blood pressure and weight remained stable. On July 30, the patient was transferred to the hospital section of the City Home to await entry into a tuberculosis sanitorium.

He has been followed in the Out-Patient Clinic. The Addison's disease seems fairly well controlled. Blood pressure is still low, averaging 95/70, but he feels well and is gaining weight. A cold abscess of the right chest wall has developed.

CASE 5. D. C., 41-year old male Negro farmer, was admitted to St. Philip Hospital on June 12, 1951. He had been treated 6 months before for tuberculous epididymitis and orchitis. Left orchidectomy and vasal ligation had been done following streptomycin treatment. Since then he had noticed progressive weakness and weight loss from 155 to 130 pounds. His family doctor had found blood pressures from 70/50 to 85/60, and suspected Addison's disease. The patient's sister stated that his skin had turned much darker in the past year.

Examination showed an intensely black Negro in no acute distress (Fig. 4). There were patches of dark pigment in the palms and soles and on the buccal mucosa, gums, and hard palate. The left testis had been removed. Blood pressure was 80/60. The lungs were clear.

Laboratory data included: urinalysis, a trace of albumin and 25 to 30 leukocytes per high power field, hemoglobin 9.8 gm.; erythrocytes 3,670,000; leukocytes 5000, with normal differential count; eosinophil count 137 per c.mm.; fasting blood sugar 78 mg. per 100 cc.; non-protein nitrogen 39 mg.; serum electrolytes normal; chest film negative; water excretion test[8], strongly positive. Eosinophils fell 38% four hours after ACTH, 25 mg. Urinary 17-ketosteroids were 2.7 mg./24 hr. Urinary corticosteroids on 4 determinations were 0.78 mg., 0.69 mg., 0.88 mg., and 0.50 mg./24 hr., all within the normal range.

FIG. 4.—(*Left*) Patient D.C. (Case 5) in 1941. (*Right*) The same patient in 1951.

The patient was thought to have Addison's disease, but of a relatively mild degree. With supplementary salt and testosterone he felt very much stronger and gained weight to 138 pounds, but blood pressure remained around 90/60. Subsequently two 75 mg. DOCA pellets and four 75 mg. testosterone pel-

lets were implanted. A salt supplement of 5 gm. daily was continued. Blood pressure rose to 100/70. The patient was discharged July 12, 1951.

He has been followed in the Out-Patient Clinic. He feels well, and weight is maintained above 140 pounds, but blood pressure is still low, around 90/60. Additional DOCA pellets are planned.

One subsequent urine culture has been reported positive for tubercle bacilli. Cystoscopy and retrograde pyelograms are normal. Further studies for genitourinary tract tuberculosis are being carried out.

CASE 6. A. D., 53-year-old Negro male, was admitted to the Richmond, Virginia, Veterans Administration Hospital on June 9, 1950. A year before he had noticed weakness and had been told his blood pressure was low. Since then he had lost weight from 180 to 120 pounds, and had noticed progressive darkening of the skin of the face and hands. Recently he had become extremely weak, and had developed nausea and vomiting.

He had been admitted to the Retreat for the Sick Hospital on May 19, 1950, in a stuporous condition, showing severe dehydration and blood pressure 60/?. Pertinent laboratory studies were: blood urea 98 mg. per 100 cc., fasting blood sugars from 59 to 65 mg.; serum sodium 129 mEq/L, serum potassium 6.5 mEq/L. Water excretion test was positive. The diagnosis of Addison's disease was made by Dr. E. P. Buxton, Jr. The patient improved after treatment with glucose and saline solution, and on June 9 he was transferred to the Veterans Administration Hospital.

Examination at this time showed the patient thin and weak, but conscious and alert. The skin generally was of a dark brown color with deeper black pigment over the forehead, dorsum of the hands, elbows, and knees (Fig. 5). The oral and nasal mucosa showed patches of bluish-black pigment. Blood pressure was 80/60. Heart sounds were faint.

Laboratory studies included: urinalysis negative; hemoglobin 7 gm.; erythrocytes 3,000,000; leukocytes 5950, with differential normal except for 5% eosinophils; serum sodium 131 mEq/L; postassium 6.5 mEq/L; fasting blood sugar 83 mg. Chest film and intravenous pyelogram were negative. Water excretion test[8] was positive. Urinary 17-ketosteroids were 4.1 mg. and 4.2 mg./24 hr.; urinary corticosteroids, 0.21 mg. and 0.38 mg./24 hr. Eosinophil count increased 9% four hours after ACTH 25 mg. Glucose tolerance test showed the following blood sugar values: fasting 97 mg. per 100 cc.; ½ hr., 127 mg.; 1 hr., 115 mg.; 2 hr., 104 mg.; 3 hr., 86 mg.; 4 hr., 53 mg.; 5 hr., 60 mg.;

FIG. 5.—Patient A.D. (Case 6) is on the right. Note darker pigment on forehead and on back of hand. The patient on the left was selected by the wife of Patient A.D. as most closely illustrating his former skin color.

6 hr., 65 mg. Tuberculin skin test (O. T. 1:10,000) was positive.

At first the patient was given supplementary salt and extra night feedings. Because he felt well, salt was withheld for 2 days. By the second day he was in Addisonian crisis, requiring vigorous treatment with glucose in saline solution, adrenal extract, and DOCA. He was subsequently regulated with DOCA 2 mg. daily and a salt supplement of 3 gm. daily. On September 22, four 125-mg. DOCA pellets were implanted. He was discharged on October 10, 1950.

He was readmitted on January 15, 1951. He had felt fairly well, but was still weak and unable to work. Blood pressure was 98/70, his weight 141 pounds, and his pigmentation unchanged. Four more 125-mg. DOCA pellets were implanted. He was discharged on February 16.

The patient now felt stronger but began to have severe cramps in the legs. He was admitted again on June 23, 1951, weighing 148 pounds. Blood pressure was 110/85. There was no edema or pulmonary congestion. Hemoglobin was now 12.8 gm. Serum electrolytes were normal. Blood urea nitrogen was 14 mg. It was thought that the muscle cramps were caused by DOCA overdosage. Salt was withheld and potassium acetate given without improvement. Oral cortisone 6.25 mg. was given every 6 hours with prompt relief of muscle cramps. Two of the last implanted DOCA pellets were removed. When cortisone was stopped, muscle cramps promptly returned. Cortisone was resumed and a dosage of 6.25 mg. orally twice a day was found to keep him free of discomfort. On this program he felt better than at any time since the onset of his illness. He was discharged October 5, 1951, to continue cortisone, feeling well enough to return to work. The black pigment on the forehead and hands has markedly faded since cortisone was begun.

Discussion. INCIDENCE. During the 10-year period from June 30, 1941, to June 30, 1951, 5 cases of Addison's disease were seen out of 60,003 Negro patients admitted to St. Philip and Dooley Hospitals. This would indicate an incidence of 1 case per 12,000 admissions in Negroes. During the same period 10 cases of Addison's disease have been seen in 94,106 white patients admitted to the Medical College of Virginia Hospital. The incidence in white patients would appear to be approximately 1 per 9,400 admissions. These figures have little statistical significance in themselves, but when they are added to similar observations by Conn and Mathews[2], and by Bergner and Eisenstein[1], it does appear that Addison's disease occurs about as frequently in the Negro as in the white race.

ETIOLOGY. All but one of the previously reported cases of Addison's disease in Negroes have been caused by tuberculosis[1]. In our 6 patients, tuberculosis is known to be present in 2 (Cases 4 and 5) and is strongly suspected in a third (Case 3). In Case 2, adrenal fibrosis and calcification were thought to have resulted from hemorrhagic destruction of the glands at the time of a previous septicemia. In Cases 1 and 6, the etiology has not been determined, the patient in Case 1 having died elsewhere, and the patient in Case 6 being still under treatment.

CLINICAL FEATURES: PIGMENTATION. The clinical features of Addison's disease in the Negro differ in no way from those seen in white patients. Only the pigmentation deserves special comment. Pigmentary changes may be quite striking, but are frequently overlooked in a race where normal pigment may vary so widely.

Of 27 patients adequately described in the literature, 21 were specifically stated to have had increased skin pigmentation. In some the skin was apparently quite black all over, but usually the pigmentation was most intense over the face, dorsum of the hands and feet, elbows, and knees. The color has been described as "ebony"[5] or "jet black"[6] in many cases, and in others as a very dark brown. The palms usually showed increased pigmentation of the skin creases and occasionally patches of pigment.

Patches of bluish-black pigmentation on the buccal mucosa, hard palate, and gums were almost universally present. These of course occur frequently in normal Negroes. Conn and Mathews[2] commented on pigmentation of the dorsum of the tongue, which is rarely seen in normal Negroes.

Our cases illustrate all of these pigmentary changes. Admittedly the selection of other patients to illustrate for photographic purposes the former color of these patients is of dubious accuracy, and the use of earlier photographs is not much better because of variations in exposure technique. However, there can be little doubt that these patients have had a definite increase in pigment. The patients in Cases 1 and 5 were almost totally black. Negroes this dark are rare in our community. Case 6 illustrates the more common pigmentation of the forehead and dorsum of the hands. All of our patients except the 2½-year-old infant (Case 2) showed various degrees of pigmentation of the oral mucosa and gums. Two patients showed pigmentation on the dorsum of the tongue.

It must be emphasized that none of these pigmentary changes is specific for Addison's disease. Every type of pigmentation described above may occur in normal Negroes. The changes produced by Addison's disease appear to be an intensification of melanin pigmentation along a pattern that is inherent in the race. The changes are quantitative rather than qualitative. The most significant clinical point is the history of deepening pigmentation. It is noteworthy that darkening of the skin apparently antedated other symptoms of Addison's disease in 3 of the patients here presented.

After cortisone was begun, there was a striking decrease in pigmentation in Case 6. At the end of 3 months on cortisone almost no black pigment remained on the forehead and hands. Two other patients received cortisone for such short periods that no such observations could be made.

Summary. 1. Six cases of Addison's disease in Negroes are presented. The diagnosis was made clinically in 5 and at autopsy in 1.

2. Statistical data are discussed which suggest that Addison's disease is about as common in the Negro as in the white race.

3. Pigmentary changes occurring with Addison's disease in the Negro are discussed.

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RHEUMATIC (VALVULAR) HEART DISEASE IN MADISON, WISCONSIN:

A Survey of Seventh Grade School Children

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The over-all prevalence of rheumatic fever in the United States is unknown, partly because it is difficult to measure. It is not a reportable disease in most states and even if it were, difficulties of correct diagnosis would tend to make reporting inaccurate. By contrast, rheumatic heart disease with its attendant valvular lesions can be recognized by cardiac examination. For this reason the examination of groups of children has been utilized to measure the prevalence of rheumatic heart disease in communities and selected groups of children. These studies are growing in number, yet in the majority of the states there has been no survey work.

Trends in morbidity rates due to rheumatic fever and mortality rates due to rheumatic heart disease are likewise difficult to visualize. On the basis of reports by Glover[1] and Knowledon[3] in England, and Wolff[9] in the United States, it appears that rheumatic fever and mortality due to rheumatic heart disease, are on the decline in both countries. Glover stated 21 years ago that rheumatic fever was an obsolescent disease, and 16 years later furnished evidence that the decline in prevalence of rheumatic fever in England was actual[1].

Two recent mortality studies in Connecticut by Haenszel[2] and the Quinns[6] have noted a similar decline in death rates due to rheumatic heart disease. In spite of evidence that rheumatic fever and mortality rates due to rheumatic heart disease are declining, rheumatic heart disease remains a public health problem of prime importance. In children and young adults, rheumatic heart disease ranks with tuberculosis as the major cause of death. In adults, rheumatic heart disease follows arteriosclerotic and hypertensive heart disease as a cause of death due to heart disease. The medical wards of most general hospitals, regardless of geographic location, are seldom without patients with rheumatic heart disease.

It is the purpose of this paper to report a study on the prevalence of rheumatic heart disease in seventh grade school children in Madison, Wisconsin. The relation of crowding in the home to prevalence was also determined. These results are documented in the hope that they may be of some value for measuring and comparing morbidity rates in the future, both in Madison and elsewhere.

Clinical Material and Methods. Description of Madison, Wisconsin. Madison, the capital of Wisconsin and county seat of Dane County, is located in the south central section of the state, 135 miles northwest of Chicago. The city is built on a narrow isthmus of land

between Lakes Monona and Mendota. It lies 845 feet above sea level at latitude 43°8'N. The annual rainfall (50-year average) is 32 inches. The average winter snowfall is 37.8 inches. The mean summer temperature is 69.7°F. The mean winter temperature is 19.5°F. Meteorologically, Madison has a short-summer type of temperate zone climate. The death rate was 6.1 per 1,000 in 1950. In the same year the birth rate was 23.8 per 1,000. The 1950 census figures are 95,594. In 1946 the population make-up was 90.1% American born, 1.3% British, 2.1% German, 2.6% Scandinavian, and 1% Italian born. New dwelling units, built in the 10-year period 1940 to 1950, numbered 4,282. Estimating 4 persons per unit, this number would house 17,128. The population increased 27,000, an indication of the housing shortage in Madison, similar to most U. S. cities. The water supply is furnished from 12 deep wells. Sewage disposal is by means of a modern disposal plant. More than 110 plants manufacturing a wide variety of goods employed 8,000 in 1946, demonstrating that the city is not fundamentally industrial in nature. It is primarily residential, with perhaps fewer areas of substandard housing than in industrial cities of comparable size. The general cultural and business life of the city is greatly influenced by 2 factors. Madison is the capital city of the state and the site of the University of Wisconsin. The surrounding county, Dane County, is chiefly concerned with dairying and is one of the largest milk producers of any county in the United States.

METHODS. A. *Organization.* The purpose of the study was explained to the nursing personnel of the Public Health Department and the Superintendent of Schools of the City of Madison. A mimeographed letter signed by the Health Commissioner (C.K.) of the City of Madison was sent to the parents of each child. This letter explained the nature and purpose of the study and requested permission to examine the child or children. No child was examined unless written permission was obtained from one of the parents.

B. *Children.* An attempt was made to examine all of the seventh-grade school children attending the public and parochial schools in the City of Madison. Of the 991 children attending the seventh grade in 17 Madison schools, 893 were interviewed and examined by the examining physician (R.Q.). Sex distribution of the children examined revealed: Males 440 (49.3%) and females 453 (50.7%). There were 8 Negro children; the remaining 885 were white. Nationality backgrounds were not determined. The mean age of the children of the study group was 12 years.

C. *Interviewing and Examining Techniques:* The nurse's room in the school, an empty classroom, or a corner of the gymnasium was the usual place of examination and interview. Identifying information and the past personal or family history of rheumatic fever, chorea, or rheumatic heart disease were recorded by the public health nurse. If a child gave an affirmative answer for a past or family history of rheumatic fever or chorea, he was questioned in greater detail by the physician. Parents were invited. If they were present, historical data were obtained from them. Only a small number of parents, approximately 40, was able to be present.

The children were undressed to the waist for the examination. Gowns were provided for the girls. Screens enclosed the examining table to ensure privacy. The physical examination was confined to the cardiovascular system. The children were examined first in the standing position. The point of maximum impulse was palpated and the presence or absence of a thrill determined. The diaphragm of the stethoscope was placed first at the 2nd right interspace along the right sternal border, then in the 2nd left interspace along the left sternal border, and then at several locations descending along the left sternal border to the 4th left interspace, then toward the apex. Next, the bell of the stethoscope was placed on the apex at the point of maximum impulse. Careful auscultation was performed in each of these locations. The observations were repeated with the child lying on an examining table. The point of maximum impulse was again determined and measured. The auscultatory maneuvers described were performed. The findings were listed and, when possible, an impression was also recorded immediately following examination.

Examinations were begun on November 6, 1950 and completed on December 15, 1950.

DIAGNOSTIC CRITERIA. *Past History of Rheumatic Fever.* When there was a history of rheumatic fever, further data could, in almost all cases, be furnished from health records kept by the public health nurse, based on information supplied by the child's family physician. Usually the child's statement could be confirmed or discounted with reasonable accuracy. When there was doubt, the child's parents were contacted and further

data obtained to establish the history of rheumatic fever as positive, negative, or doubtful. Unless there was clear evidence of past rheumatic fever, it was not recorded as such.

Family History of Rheumatic Fever. The history (confirmed when possible by the child's parents) of rheumatic fever, in either parent or siblings, was recorded as "positive."

Normal Heart. When the heart sounds were normal without murmurs or evidence of enlargement, unusual arrhythmia, or other cardiac abnormalities, the child was classified as having a normal heart.

Unexplained or Functional Murmur. These murmurs were soft, grade 1 or 2, systolic in time, and were located most frequently at the base of the precordium in the 2nd left interspace along the left sternal border. Approximately 85% of the so-called unexplained murmurs were heard in this location. They were heard next most frequently medial to the apex and least frequently along the left sternal border in the 3rd interspace. These murmurs were not accentuated by exercise or change in position, and frequently became inaudible on changing position. They varied with respiration, that is, tended to become fainter on inspiration and were not transmitted. The second pulmonic sound was not accentuated.

The "apical" murmurs had none of the characteristics of murmurs usually associated with mitral insufficiency, although it is realized that these innocuous-sounding so-called functional murmurs are occasionally heard in patients with mitral insufficiency.

Congenital Heart Disease. It is not always possible to establish an anatomical diagnosis of congenital heart disease on the basis of signs and symptoms. However, when the murmur and physical findings were characteristic, this diagnosis was made.

Possible Congenital Heart Disease. When the cardiac findings were strongly suggestive but not absolutely characteristic of congenital heart disease, the term, "Possible Congenital Heart Disease," was applied. Occasionally it was extremely difficult to decide whether a murmur was a so-called "unexplained murmur" or was associated with a congenital cardiac lesion. A few were classified "Possible Congenital Heart Disease," the rest "Unexplained Murmurs."

Mitral Insufficiency. This diagnosis was made when a moderately loud to very loud (grade 3 or louder) high-pitched, early systolic murmur was heard at the apex and transmitted toward or into the axilla. The second pulmonic sound was always louder than the aortic second sound and it was often accentuated. Exercise increased the intensity of the murmur and it was usually heard best with the patient in the left recumbent position. Occasionally a thrill was felt at the apex. The presence of cardiac enlargement was not required to establish the impression of mitral insufficiency.

Mitral Stenosis. The findings required for the diagnosis of mitral stenosis were a grade 2 to 4, soft to moderately loud, low-pitched, rumbling, presystolic murmur heard at the apex with or without a mid diastolic component. These murmurs were heard best through the bell of the stethoscope. The second pulmonic sound was accentuated. Often a thrill could be felt at the apex. Exercise increased the intensity of the murmur. When the presystolic rumble was blended into the first sound, or the first sound was "buried" in the rumble and a systolic murmur with the characteristics described under mitral insufficiency followed immediately, the diagnosis of "Mitral Stenosis and Insufficiency" was made.

Rheumatic Heart Disease and Congenital Heart Disease. In children, when clear-cut findings of both rheumatic valvular lesions and congenital cardiac defects were demonstrated, the diagnosis of "Rheumatic and Congenital Heart Disease" was made.

Possible Rheumatic Heart Disease. Occasionally systolic apical murmurs were heard in children without a past history of rheumatic fever which were strongly suggestive but not diagnostic of valvular heart disease. These murmurs could not be classified with certainty as either functional or organic, yet they suggested the latter type more strongly than the former. Children with murmurs of this type were listed as having "Possible Rheumatic Heart Disease." It is this type of murmur located at the apex which is extremely difficult to classify. If they are all classified as functional or unexplained, many would undoubtedly be classified incorrectly. Likewise, if they are all called organic many incorrect diagnoses of valvular heart disease would be made. It was impossible, under the conditions of the survey examinations, to be certain of the significance of these murmurs. Even under ideal conditions with the aid of electrocardiography, orthodiascopy, Roentgen-ray and fluoroscopy, it is not always possible to be sure of the diagnosis of valvular heart disease in some patients. For this reason children with this type of murmur were listed as having "possible rheumatic heart disease." In this category possibly

there were children with valvular heart disease and some with true so-called unexplained or functional murmurs, but by placing all these children in this category it is hoped that errors of omission have balanced errors of commission.

Crowding in the Home. Two different criteria for crowding in the home were employed: 1) more than one person per room; 2) more than 1.5 persons per room.

matic heart disease group, the rate then becomes 2.8%. As a result of a report sent home to the parents of the children examined and home visits by the public health nurses, most of the children classified as having congenital heart disease, possible congenital heart disease, rheumatic heart disease, pos-

TABLE 1.—RESULTS OF CARDIAC EXAMINATIONS OF 893 SEVENTH-GRADE SCHOOL CHILDREN OF MADISON, WISCONSIN

Impression	*Number of Children*	*% of Total No. of Children*
Normal Cardiovascular System	491	54.9
Unexplained Murmur	317	35.5
Congenital Heart Disease	4	0.4
Possible Congenital Heart Disease	20	2.2
Potential Rheumatic Heart Disease	14	1.6
Possible Rheumatic Heart Disease	22	2.5
Rheumatic Heart Disease	20	2.2
Rheumatic and Congenital Heart Disease	5	.7
Totals	893	100.0

Results. The data obtained by examination are tabulated in Table 1. Of the 893 children examined, 491 (54.9%) were classified as normal, that is, had normal cardiovascular systems; 317 (35.5%) had unexplained (functional or physiologic) murmurs; 4 children (0.4%) were thought to have congenital heart disease; 20 (2.2%) were classified as having possible congenital heart disease; 14 (1.6%) had potential rheumatic heart disease, that is, gave a history of having had rheumatic fever but at the time of examination had no evidence of valvular heart disease, and 22 (2.5%) had possible rheumatic heart disease. Twenty children (2.2%) had evidence of valvular heart disease; they were classified as having rheumatic heart disease. The rheumatic heart disease rate, therefore, in this group of children at this time was 2.2%. If the 5 children who were thought to have both rheumatic and congenital heart disease are added to the rheu-

sible rheumatic heart disease, and congenital and rheumatic heart disease were promptly seen and examined by their family physicians or referred by the family physician to a pediatrician or cardiologist for more complete examination than could be given under the conditions of the survey. The fact, that in the majority of cases the impression of the survey physician agreed with the diagnosis of the pediatrician or cardiologist, would suggest a high percentage of agreement between the impression and diagnosis. The anatomical diagnoses of the valvular defects of the 20 children classified as having rheumatic heart disease are shown in Table 2. There were 11 children with mitral insufficiency, 7 with mitral stenosis, and 2 with mitral stenosis and insufficiency. No diagnoses of aortic insufficiency were made.

Correlation of the clinical impression with the past history of rheumatic fever, chorea, and possible rheumatic

fever is shown in Table 3. Twelve children gave the history of having had rheumatic fever. Of these, 10 now have valvular heart disease and 2 were believed to have a normal cardiovascular system. One who had chorea now has valvular heart disease. Of 6 who gave a history suggestive but not diagnostic of rheumatic fever, 2 have valvular

The housing status in relation to crowding in the home of the rheumatic and non-rheumatic children was determined and is shown in Figure 1. Of the 34 rheumatic children (children with rheumatic heart disease or a history of rheumatic fever) 8% lived in homes with 1.5 or more persons per room, 18% in homes with 1 or more

TABLE 2.—VALVULAR DEFECTS OF 20 CHILDREN WITH RHEUMATIC HEART DISEASE

Impression	*No. of Cases*	*%*
Mitral Insufficiency	11	55.0
Mitral Stenosis	7	35.0
Mitral Stenosis and Insufficiency	2	10.0

TABLE 3.—PAST HISTORY OF RHEUMATIC FEVER, CHOREA, POSSIBLE RHEUMATIC FEVER OR NO RHEUMATIC FEVER CORRELATED WITH PRESENCE OR ABSENCE OF RHEUMATIC HEART DISEASE

Past History	*Rheumatic Fever*		*Chorea*		*Possible Rheumatic Fever*		*No Known Rheumatic Fever*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Rheumatic Heart Disease	10	40	1	4	2	8	12	48
Normal Heart	2				4			

(rheumatic) heart disease and 4 do not. A total of 13 (52%) of the 25 children with rheumatic heart disease gave a past history of rheumatic fever, chorea, or possible rheumatic fever. In 12 (48%) with rheumatic heart disease, a history of rheumatic fever, chorea, or possible rheumatic fever could not be elicited.

As in previous studies, a high familial incidence of rheumatic fever was noted. The family history was positive in 8 of 39 children (20.5%) with rheumatic heart disease, rheumatic and congenital heart disease, or the past history of rheumatic fever (potential rheumatic heart disease). Of the children classified as normal by the methods employed, 47 (5.6%) had a positive family history.

persons per room, and the remainder (74%) lived in non-crowded homes. Of the non-rheumatic children, 6% lived in homes with 1.5 or more persons per room, 26% in homes with one or more persons per room, and the rest (68%) in non-crowded homes. These results give the impression that crowding did not characterize the homes of the rheumatic children as often as the non-rheumatic children, although the difference between the two is not significant. It should be noted, also, that the number of rheumatic children is so small that comparison with the much larger number of non-rheumatic children is hazardous.

Next, the rheumatic and non-rheumatic groups of children were considered, and the per cent who lived in

crowded and non-crowded homes calculated (FIG. 2). This figure shows that of the 497 children who lived in non-crowded homes, that is, homes with less than 1 person per room, 4.7% were rheumatic and 95.3% were non-rheumatic. Of the 220 children living in homes with 1 or more persons per room, 3.2% were rheumatic and 96.8% were non-rheumatic. Of the 54 children living in homes with 1.5 or more persons per room, 5.6% were rheumatic and 94.4% were non-rheumatic. These figures seem to indicate that crowded homes in Madison in 1950 are no more likely to house rheumatic children than are non-crowded homes.

There were no significant differences between the rheumatic heart disease rates found in children from any of the 17 schools. In 2 of the 3 largest schools, East High School and Central High School, the average number in the family and the average number living in the homes of the children examined was considerably greater than for children in the other 15 schools. There was more crowding, on the average, in the homes of the children from these two schools. However, the prevalence of rheumatic heart disease was not increased in these high schools when compared with other schools.

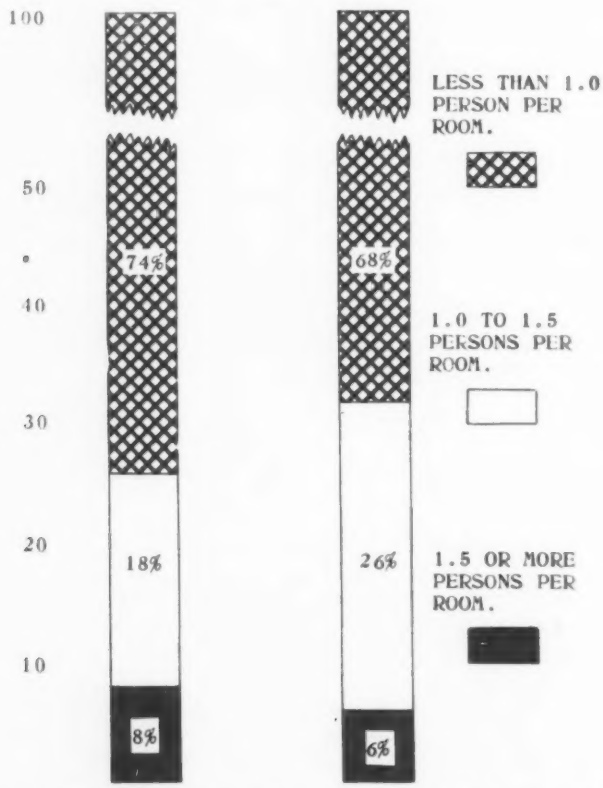

FIG. 1.—Housing status in regard to crowding in the home of rheumatic (left column) and non-rheumatic children (right column). Figures at left, percentage of children.

Discussion. As long as there are clinicians there will be differences of opinion regarding the interpretation of cardiac murmurs. Keeping in mind that it is impossible to achieve 100% accuracy in this type of examination, the results of this study indicate that the prevalence (2.2%) of rheumatic heart disease and rheumatic fever in seventh grade school children in Madison, Wisconsin, in 1950 is about the same as that observed by the same examiner in a group of urban children of a similar age group (2.45%) in 4 Connecticut cities (Ansonia, Bridgeport, Hartford and Waterbury)[7]. The rate, 2.2%, was slightly more than twice that observed in fifth, sixth, seventh, and eighth grade white and Negro children living in the town of Dublin, Georgia, in 1945[4] and over 4 times as high as that reported in Dade County, Florida[8]. These findings are in keeping with the general belief that the prevalence of rheumatic fever and rheumatic heart disease is higher in the northern than in the southern sections of the United States. Rheumatic heart disease rates for Madison are as high as any reported from various areas of North America.

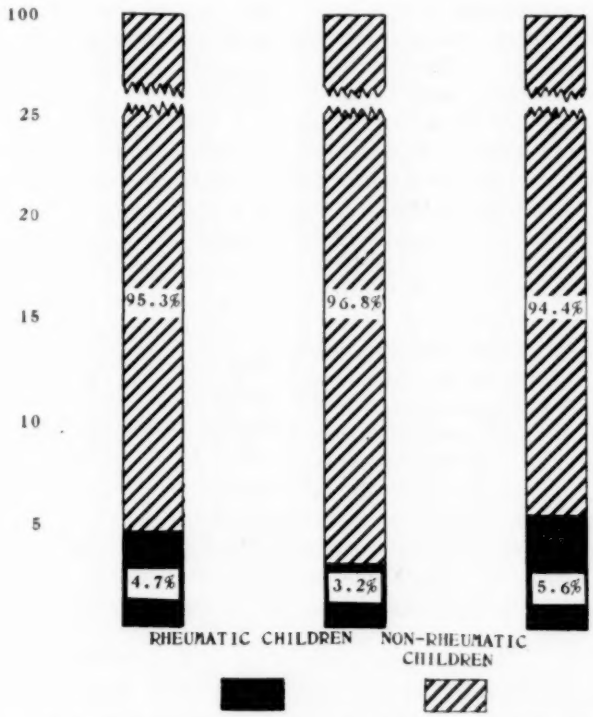

FIG. 2.—Percentage of rheumatic and non-rheumatic children living in crowded and non-crowded homes. Column at left, less than 1.0 person per room; center column, 1.0 to 1.5 persons per room; column at right, 1.5 or more persons per room.

Crowding in the home did not appear to influence the prevalence of rheumatic heart disease in Madison. In this regard the findings are at variance with those in a primarily residential city, Milford, Connecticut, where housing was predominantly good; but

crowding, where it existed, was thought to exert a significant effect on the prevalence of rheumatic heart disease[5]. However, in 3 other industrial Connecticut cities (Ansonia, Derby, and Shelton) where poor housing conditions and crowding were unusually common, both of these factors seemed to have some relationship to the very high rheumatic heart disease rate of 6%. In the Connecticut cities 41.3% of the rheumatic children and 31.4% of the non-rheumatic children lived in homes with more than 1 person per room. These percentages are somewhat higher than those found in Madison in 1950, where 18% of the rheumatic children and 26% of the non-rheumatic children lived in homes with more than 1 person per room.

The close relationship between the epidemiology of respiratory infections due to the beta hemolytic streptococcus and rheumatic fever is well known. In addition, it is an old clinical observation that rheumatic fever is almost always preceded by a respiratory infection due to the beta hemolytic streptococcus. Crowding in the home is only one of many factors which might influence the frequency of acute respiratory infections due to the beta hemolytic streptococcus. Of more specific importance may be crowding in the bedroom or bed. The opportunities for all children in Madison to acquire a beta hemolytic streptococcal infection in school rooms, buses or theaters are probably about equal, regardless of the home environment.

Summary. 1. In Madison, Wisconsin, 893 seventh grade school children were interviewed and examined to determine the incidence of rheumatic heart disease in this group of children.

2. The rheumatic heart disease rate was found to be 2.2%. If 5 children who were thought to have both rheumatic and congenital heart disease are included, the rate becomes 2.8%. These findings would seem to indicate that the prevalence of rheumatic heart disease in Madison school children at this time is as high as that reported for children of similar age from any other section of the United States.

3. Crowding in the home did not appear to influence the prevalence of rheumatic heart disease. A significant difference was not observed between the numbers of rheumatic and non-rheumatic children who lived in crowded homes.

4. A high familial incidence of rheumatic heart disease was noted.

Acknowledgements. Miss Vivian Holland and the Staff of the Statistical Service Division of the Wisconsin State Board of Health recorded and analyzed the data on machine tabulating cards. Miss Evelyn Nelson and the Staff of the Public Health Nurses of the Madison Department of Health assisted at all interviews and examinations of the children. Mr. Philip H. Falk, Superintendent of Schools, the School Board, and the teachers of both the public and parochial schools were most cooperative. It is a pleasure to acknowledge the help of all these individuals.

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I_{131} UPTAKE IN TREATED HYPERTHYROIDISM*

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WITH the introduction of sensitive gamma ray detectors, notably the scintillation counter[2], and the administration of doses as small as 1 microcurie (mcc.) of I_{131} orally[1], it has become possible to repeat diagnostic tracer studies several times without hazard to the patient.

The purpose of this report is to stress the important diagnostic information which may be obtained by repeated uptake readings within the first 24 hours, particularly by uptake studies 3 and 6 hours after administration of the tracer dose.

Method and Material. The instrumentation and technique have been described in detail elsewhere[1]. Doses of 1 or 2 mcc. of carrier-free I_{131} were administered intravenously or orally. Uptake determinations were performed at 30 minutes, 1 hour, 3 hours, 6 hours, 24 hours, and 48 hours after the administration of the diagnostic tracer dose.

Sixty hyperthyroid patients were studied. Thirty-two of them were treated in this hospital with therapeutic doses of I_{131}, 6 by operation, 4 with thiourea derivatives, and 1 solely with Lugol's solution. Most of the patients treated by operation or I_{131} had taken thiourea drugs or Lugol's solution at one time or other in the course of their disease. The remainder of the patients studied, but not treated here, gave a history of unequivocal hyperthyroidism in the past and were in the hospital for unrelated conditions at the time tracer studies were performed. Of these 17 patients, one had been treated with I_{131} elsewhere and the others had been thyroidectomized following preparation with Lugol's solution and thiourea drugs.

Results. NORMAL SUBJECTS. It became apparent in the beginning of the study that the oral route of administration could be substituted for the intravenous route. The subjects were given a light breakfast. Twenty-seven healthy controls were given 1 or 2 mcc. of carrier-free I_{131} intravenously. The same amount of I_{131} was given to the same individuals several weeks later orally and no appreciable difference was found in the 3, 6, 24, and 48-hour pick-up values between the 2 routes of administration.

The shaded area in Fig. 1 demonstrates the observed range of the uptakes in 88 healthy controls (43 were given intravenous doses and 45 oral doses) plotted on semilogarithmic paper.

HYPERTHYROID PATIENTS. Rapid accumulation of I_{131} by the thyroid gland could be demonstrated in all untreated patients, regardless of the total amount of I_{131} accumulated by the thyroid. It was found in all of our patients that more than 2/3 of the total I_{131} accumulated in 24 hours was present in the gland within 6 hours. In the controls the 6 hour to 24 hour ratio was 62.2% $\pm$9.6.

Hyperthyroid patients treated in this hospital were followed clinically and by repeated tracer studies, protein bound iodine, basal metabolic rate, and serum cholesterol determinations.

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions of the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

It became apparent that with clinical improvement, drop in protein bound iodine and basal metabolic rate, and rise in serum cholesterol, the maximum amount of I_{131} picked up by the thyroid returned to normal. However, *the rate of accumulation by the thyroid remained rapid.* As a matter of fact, even with complete clinical and laboratory evidence of remission the amount accumulated by the thyroid in 6 hours was in excess of 2/3 of the total 24-hour uptake.

Some illustrative cases follow:

Case Reports. CASE 1. L. P. GH 18542, is a 33-year old white man with moderately severe Graves' disease. In September, 1950, the protein-bound iodine was 11.3 micrograms (mcg.) per 100 cc., the basal metabolic rate plus 1%, and the serum cholesterol 142 mg. per 100 cc. (Fig. 2). The solid line and upper interrupted line demonstrate thyroid pick-up of 2 tracer doses 2 weeks apart, in both instances showing maximum uptake in 6 hours. The patient was treated on September 21, 1950, with 4.25 millicuries of I_{131} (7000 r.e.p. per gram of thyroid tissue). In May, 1951, he was clinically well and working as an aircraft mechanic. The lower interrupted line represents a tracer study after therapy. Protein-bound iodine was 5.8 mcg. per 100 cc.,

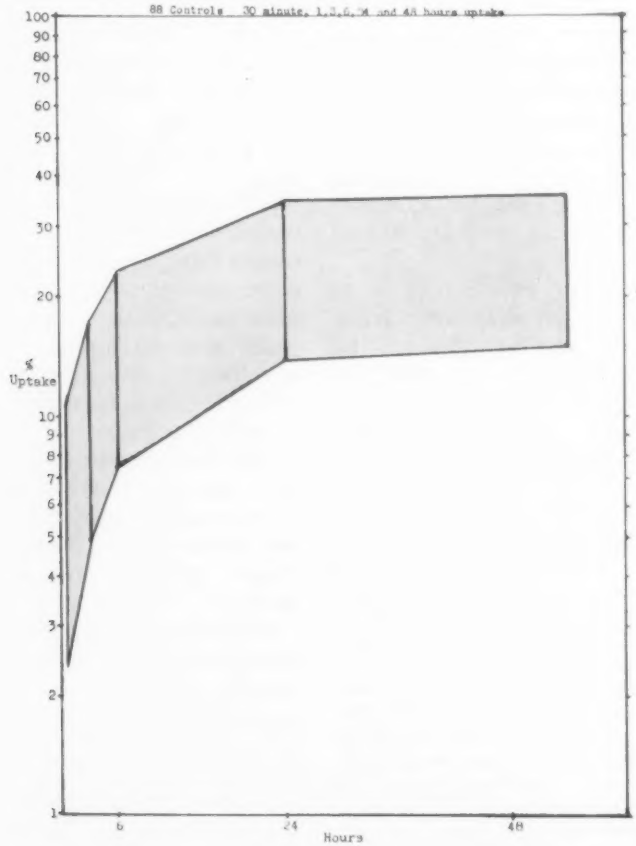

FIG. 1.—Range of I_{131} uptake in 88 healthy controls at 1, 3, 6, 24, and 48 hours.

basal metabolic rate plus 14%, and serum cholesterol 232 mg. per 100 cc. (The basal metabolic rate may represent a laboratory error.) Again the maximum uptake was reached in 6 hours.

CASE 2. C. B., GH 23201, is a 30-year old white man with severe Graves' disease. Protein bound-iodine was 8.3 mcg. per 100 cc., basal metabolic rate plus 57%, and serum cholesterol 90 mg. per 100 cc. at the time of the first tracer study on March 13, 1951 (Fig. 3). The patient was treated with 8.23 millicuries of I_{131} on March 23, 1951 (7000 r.e.p. per gram thyroid tissue). On June 4, 1951, the patient was back at work as a railroad worker. Protein-bound iodine then was 4.1 mcg., basal metabolic rate minus 19%, and cholesterol 280 mg. On October 3, 1951, the patient was clinically euthyroid, the basal metabolic rate was minus 14%, and serum cholesterol 280 mg. Note rapid rate of uptake with total amount taken up within normal range.

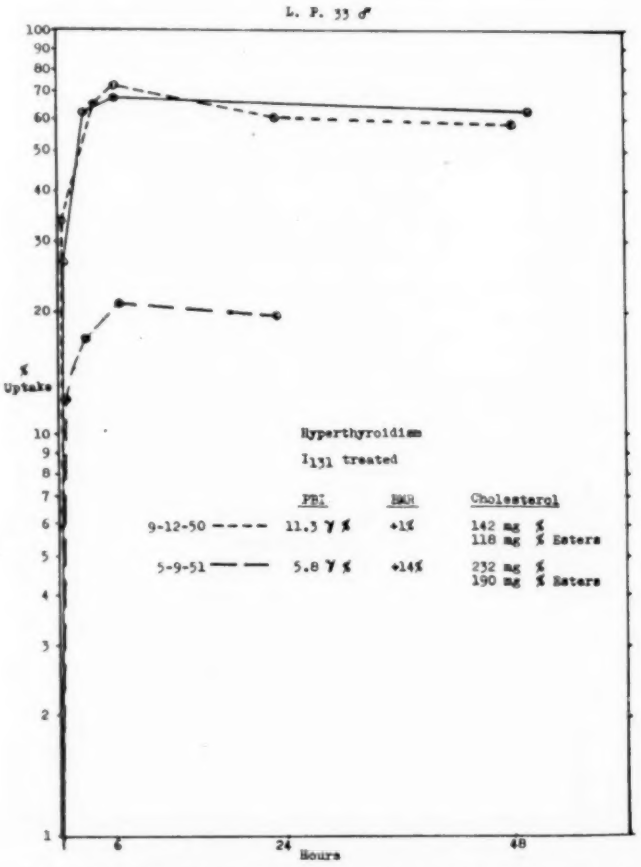

FIG. 2.—I_{131} uptake in hyperthyroid patient (Case 1), showing initial tracer dose, therapeutic dose, and subsequent tracer dose.

CASE 3. D. S., a 29-year old white woman with moderately severe hyperthyroidism, was prepared for thyroidectomy with Lugol's solution (Fig. 4). She took Lugol's solution for about 8 weeks. She went into a complete clinical remission.

The first tracer study was performed 4 weeks after discontinuation of Lugol's solution. For personal reasons, operation was not

performed and the patient remained clinically well. The second tracer study was done 3 months after discontinuation of Lugol's solution.

CASE 4. J. U., GH 13129, a 31-year old man, had severe Graves' disease in 1944 and underwent a subtotal thyroidectomy. At the time of the diagnostic tracer study (February, 1951) he was clinically well and working. His protein-bound iodine was 5.0 mcg. per 100 cc., basal metabolic rate plus 9%, and serum cholesterol 291 mg. per 100 cc. Note the rapid accumulation of I_{131} in the thyroid.

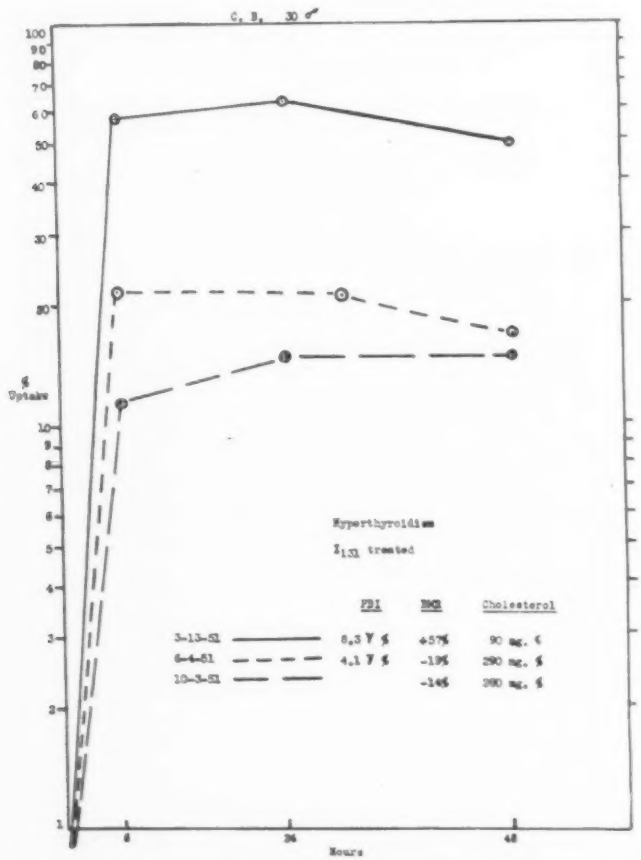

FIG. 3.—I_{131} uptake in hyperthyroid patient (Case 2), showing therapeutic dose and 2 subsequent tracer doses.

Discussion. The rapid rate of accumulation of I_{131} by the hyperactive thyroid gland has been demonstrated before[4,5,6,8]. The plotting of the absolute values in per cent of the administered dose on semilogarithmic paper has been found to demonstrate satisfactorily the features of interest.

It is not surprising that the rapid rate of I_{131} pick-up persists in surgically treated hyperthyroid subjects who appear clinically euthyroid. Whatever amount of thyroid gland is left in the patient by the surgeon is still hyperthyroid tissue.

Similar considerations prevail in I_{131} treated patients in whom a rapid

rate of uptake persists[9]. Quimby and Werner[7] stated that the non-uniform deposition of I_{131} in thyroid glands results in focal areas of intense radiation with some tissue remaining structurally and functionally intact. External radiation (Roentgen-ray), however, is relatively uniform. Unfortunately, no Roentgen-ray treated hyperthyroid patients were available for study. Gorbman[3] found survival of follicles in mice which had been given 2 microcuries of I_{131} per milligram thyroid tissue. This dose is about 4 times as great as the therapeutic doses in man (7000 r.e.p. per gram of tissue).

The effect of iodide and thiourea derivatives is thought to be due to inhibition of hormone production. Their action is chiefly within the thyroid cell. It is not yet generally agreed why administration of iodides (for example, Lugol's solution) produces remission regularly, only to lead to aggravation of signs and symptoms later on. Whether these remissions represent

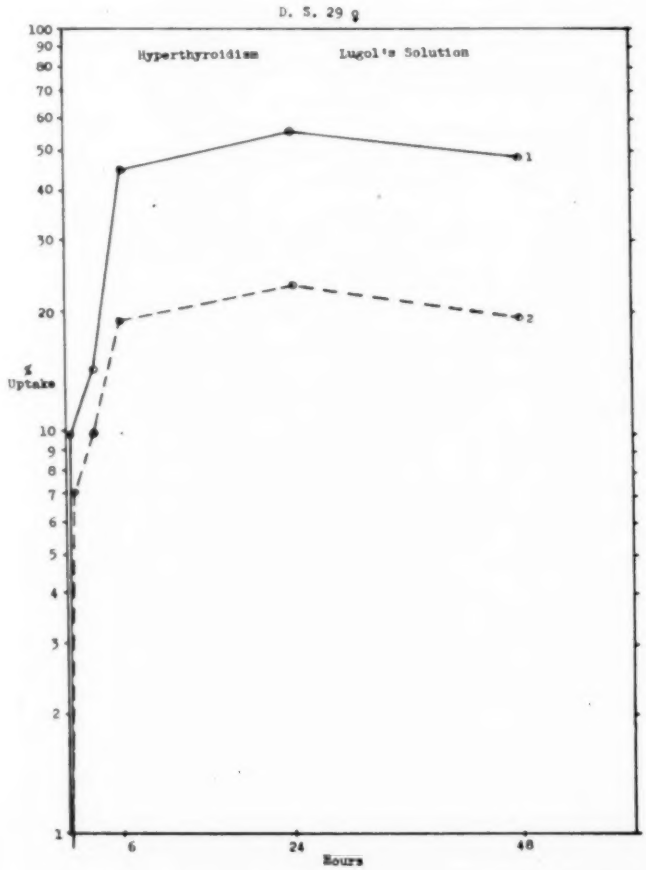

FIG. 4.–I_{131} in hyperthyroid patient (Case 3), showing tracer doses before and after the use of Lugol's solution.

fluctuations peculiar to hyperthyroidism or whether they are due to "iodine fastness" has not been established. It is agreed that thiourea drugs produce remissions and that recurrences after discontinuation of therapy with these drugs are quite common.

suspected because of the presence of one or two signs or symptoms, such as tachycardia or heat intolerance, and in whom the total amount of I_{131} accumulated was within the normal range, but whose rate of uptake was rapid. Protein-bound iodine, basal

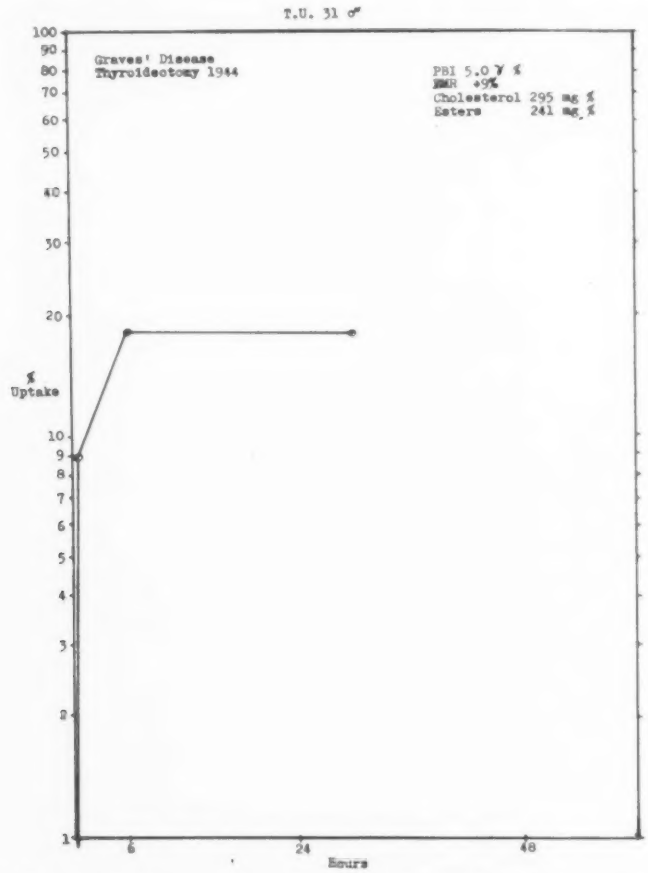

FIG. 5.–I_{131} uptake 6 years after thyroidectomy for Graves' disease (Case 4).

After successful treatment, the persistent rapid rate but reduced total amount of I_{131} uptake indicates only quantitative and not qualitative changes in the thyroid gland with regard to its avidity for I_{131}.

We have recently observed several subjects in whom hyperthyroidism was

metabolic rate, and serum cholesterol determinations were normal or equivocal. It is possible that this rapid rate of uptake represents an inherent functional disturbance in the thyroid gland. Prolonged study of these subjects is being undertaken. They are being followed clinically, by determinations of

protein-bound iodine, basal metabolic rate, and serum cholesterol. They will be given diagnostic I_{131} tracer doses to see whether the rate of uptake and total amount of I_{131} accumulated remains the same, whether the rate of uptake regresses, or whether it and the total pick-up increase.

Family members of our hyperthyroid patients are being studied by means of I_{131} diagnostic tracer doses in order to detect abnormalities in the rate of uptake.

Summary. 1. Sixty patients with active hyperthyroidism or a history of past hyperthyroidism were studied by means of repeated I_{131} thyroid uptake studies.

2. Previous observations by other investigators on the initial rapid rate of accumulation of I_{131} by the thyroid were confirmed.

3. Treated hyperthyroid patients in remission were found to have a reduced total amount of I_{131} accumulated by the thyroid but retained their rapid rate of uptake.

4. Several patients with suspected hyperthyroidism were studied and their thyroids found to accumulate a normal maximum amount of I_{131}, but to have a rapid rate of uptake. These patients are being followed.

5. The importance of obtaining repeated uptake readings within 24 hours after administration of the tracer dose of I_{131}, particularly at 3 and 6 hours, is stressed.

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EFFECTS OF RADIOACTIVE COLLOIDAL GOLD (AU_{198}) ON GUINEA PIGS

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Because of the few histologic reports of the effect of radioactive gold (Au_{198}) on tissues after intraperitoneal instillation, it is felt that additional histopathologic studies, as well as distribution studies, of its effect upon the tissues of the guinea pig, would be of value. These studies assume greater significance since this agent is being used clinically more frequently in the therapy of malignant disease.

P. F. Hahn[7,10,15] has administered it to patients having carcinoma of the breast, lymphoblastomas, prostatic and vesical neoplasms, metastatic carcinoma in the liver, and neurogenic sarcoma. Portmann and Hays[13] have used this agent in the treatment of undifferentiated carcinoma of the thyroid, cystic gliomas, cerebral hemangioblastoma, and peritoneal carcinomatosis secondary to ovarian carcinoma. Since radioactive gold, after administration, is found to be present in organs proportionate to their quantity of reticuloendothelial cells, it has been used in diseases of the reticuloendothelial system[14]. This agent also has been proposed for the treatment of cervicouterine carcinoma and malignancies of hollow viscera[1,17]. It has been administered intravenously, intrapleurally, intraperitoneally, and by direct infiltration of the tumor-bearing area. There have been no reports of toxicity other than that expected from comparable doses of irradiation by other methods. Hadden[5] as well as Hahn[7] suggest the toxicity to be even less than that of the usual forms of radiation therapy. Hahn holds great hope for the use of radioactive gold in the treatment of malignant disease because its insolubility permits local instillation; it is well understood chemically, and there is no problem in handling radioactive excreta, since it is not excreted by the human body in significant amounts. Williams *et al.*[18], have called attention to the facts that it provides a means of therapy in cases where the skin would be a limiting factor in external irradiation and that it can be administered as an outpatient procedure.

Williams *et al.*[18], showed that after radioactive gold was administered intraperitoneally or intracardially in rats and mice it was chiefly found in liver, spleen, bone marrow, lungs, kidneys, colon, thymus, heart, and skeletal muscle. Sheppard *et al.*[16], found similar distribution in humans. No histologic details accompanied their reports. Sherman, Nolan, and Allen[17], studied the effect of this agent on the tissues of the rabbit after parametrial instillation. They found that after 72 hours there was an increase in lymph vessels

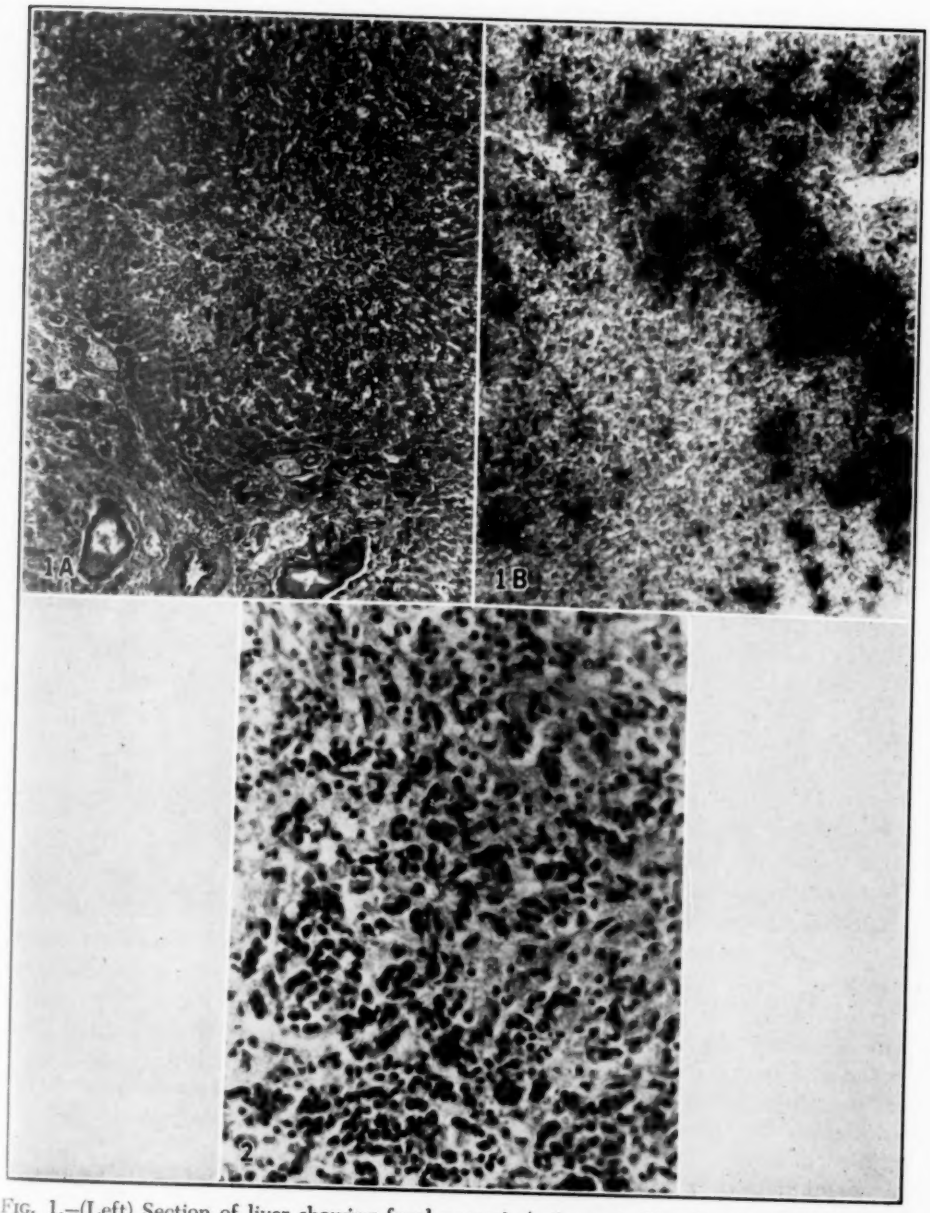

FIG. 1.—(Left) Section of liver showing focal necrosis (guinea pig No. 1) x 70. (Right) Micro-radio-autogram of liver showing clump-like arrangement of radioactivity (guinea pig No. 1) x 70.

FIG. 2.—Section of spleen demonstrating myeloid metaplasma (guinea pig No. 3) x 250.

and that phagocytes contained gold as demonstrated by microradio-autographs and micro-incineration studies of these tissues. Further, many lymph follicles in the parametrial tissues were enlarged and phagocytes containing gold were found entering into their substance. In areas where the radioactive gold was most abundant, there was severe cellular destruction. Seven days after injection, radioactive gold after intraperitoneal instillation failed to reveal the presence of radioactive gold in the liver or spleen after 2 weeks, but there was extreme radiation effect in the retroperitoneal lymph nodes. No significant changes in the abdominal viscera were observed. In another experiment these same investigators used oxycel impregnated with radioactive gold about the pelvic vessels and cornua of the uterus of the

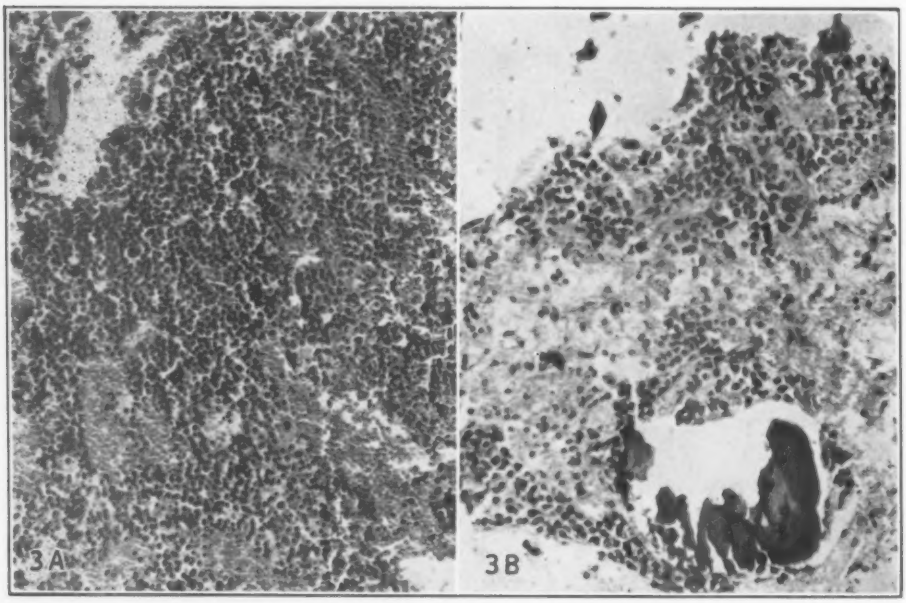

FIG. 3.—(Left) Vertebral marrow of control x 125. (Right) Vertebral marrow demonstrating hypoplasia (guinea pig No. 2) x 125.

was increased in phagocytes as well as in the iliac lymph nodes, with evidence of "radiation damage". Six weeks after instillation the iliac lymph nodes remained damaged, although focal areas of regeneration were noted. Three months after injection there were pronounced fibrosis and atrophy of cell structures. Sherman *et al.* commented that after parametrial instillation there was no untoward radiation effect locally or distally. Studies conducted rabbit. They found fibrosis about these structures 6 weeks after application. Many of the retroperitoneal lymph nodes were necrotic. Assay of the radioactivity in various organs revealed a minimal degree compared to that of the treated area. Microscopically there was minimal necrosis in the treated area with much fibrosis.

Sherman, Nolan, and Allen[17] injected radioactive gold into the uterine cavity. Atrophy of the endometrium

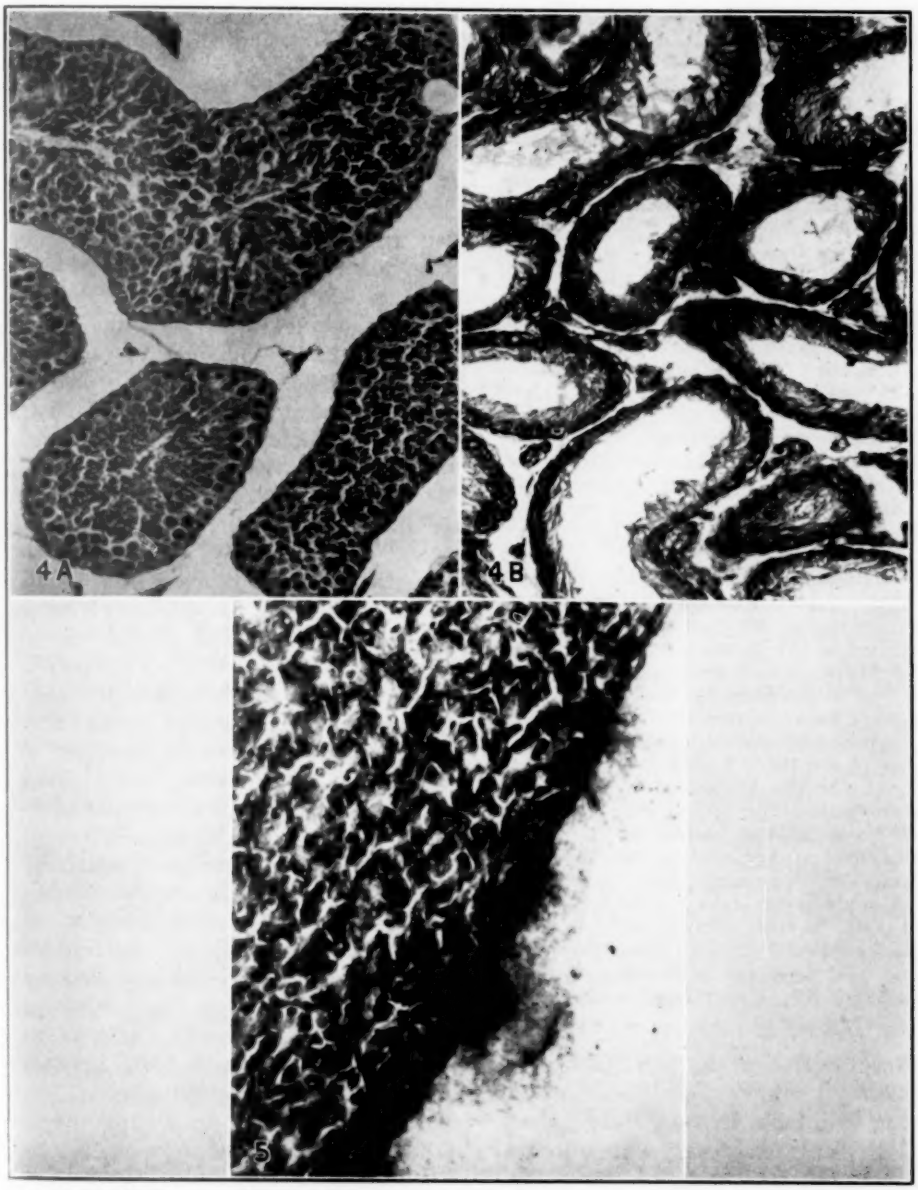

FIG. 4.—(Left) Section of testis of control x175. (Right) Section of testis of guinea pig No. 7 showing hypoplasia x 175.

FIG. 5.—Microradio-autogram demonstrating foci of activity in capsule of pancreas (guinea pig No. 5) x 250.

resulted and after a second administration there was a decrease in the number of primordial follicles in the ovaries.

Procedure. Seven male guinea pigs were used as test animals and 3 as controls. Their weights ranged from 315 to 480 gm. Each was maintained on a stock laboratory diet. Four cubic centimeters (1 mc./cc.) of radioactive colloidal gold (Au_{198})* were instilled intraperitoneally after cleansing and applying tincture of iodine to 4 of the test animals. Two cubic centimeters (1 mc./cc.) were instilled in a similar fashion to 2 test animals, and 1 test animal received 3 cc. Control animals received 4 cc. of non-radioactive colloidal gold (Au_{198}) intraperitoneally. Dosage in equivalent Roentgen units was obtained by formulae devised by Marinelli *et al.*[12].

Periodic activity counts were made with the end-window type of Geiger-Mueller counter both with and without a 1-mm. aluminum filter at 50-cm. distance. Body weights were recorded at intervals.

Complete autopsies were performed on all animals. Gross radioautographs were made on portions of all tissues obtained. Tissue was fixed in 10% formalin as well as Zenker's fluid. Microradio-autographs were made after the method described by Axelrod, and direct counts of tissue radioactivity on sections were made from formalin-fixed material. The processing of the tissue for histologic study was done in a routine manner except that paraffin instead of tissue mat was used for imbedding. The latter material was noted to produce artifacts when employed in the production of microradio-autographs. Sections for histologic study were stained with hematoxylin and eosin. Sections used for radioautography were counterstained with hematoxylin and picric acid after the radioautographs were completed. All sections were cut 5 microns in thickness.

Results. HISTOLOGIC AND RADIOAUTOGRAPHIC OBSERVATIONS. Sections of brain, eye, lung, thyroid, liver, spleen, omentum, pancreas retroperitoneal lymph nodes, portions of the gastrointestinal tract, adrenals, kidneys, testes, skin, psoas muscle, and vertebral, and in several instances sternal, bone marrow were studied. All tissues were compared with those of the control animals. Only positive histologic microradio-autographic findings will be reported.

Guinea pig No. 1 received 4 mc. of radioactive gold (909.9 equivalent Roentgens (e.r.) + 6.86 Roentgens (r.)) or 916.76 total r., and was found dead 6 days after instillation. The liver revealed focal necrosis of hepatic cells. Sections of testicle showed absence of spermatozoa and spermatids. Microradio-autographs of the liver demonstrated dense foci of activity most marked in the zones revealing hepatic necrosis. Although activity was evident in the lung and spleen, there was no specific localization as to site. Activity was observed to be distributed for the most part in dense localized masses approximately 50 microns in diameter.

Guinea pig No. 2 also received 4 mc. of radioactive gold (957.4 e.r. + 7.02 r, or 964.4 total r). The animal survived 13 days. The testes revealed absence of spermatozoa, with few spermatids in the tubules. Sections of vertebral bone marrow revealed a moderate reduction in all cellular components, with a moderate relative increase of loose areolar connective tissue in the marrow cavity. Radioautographs demonstrated activity in the spleen, especially in the regions of the splenic sinuses. Focal activity was observed in the retroperitoneal lymph nodes and liver. There was no focal hepatic necrosis seen in this animal. Microradio-autographs revealed activity to be of a similar pattern to that seen in guinea pig No. 1.

Guinea pig No. 3 also received 4 mc. of radioactive gold (914.3 e.r. + 6.89 r., or 921.1 total r) and succumbed on the 23rd day. As previously observed, there was focal hepatic ne-

*Obtained from Abbott Laboratories, Chicago, Illinois (permission of Atomic Energy Commission).

crosis present. In addition, zones of hematopoiesis were found in the hepatic sinusoids. Similar zones of hematopoiesis were noted in the spleen. The testes revealed absence of spermatozoa, with a few spermatids in the testicular tubules. Slight focal adrenal cortical necrosis was observed. Microradio-autographs failed to reveal any evidence of tissue activity.

Guinea pig No. 4 received 3 mc. of radioactive gold (674.08 e.r. 6.89 r or 680.97 total r), and survived 26 days following administration. Sections revealed areas of hematopoiesis in the spleen. The liver showed foci of granulocytopoiesis in the portal regions. No zones of hepatic necrosis were noted. Absence of spermatozoa was observed in the testicular tubules, although spermatids were present in moderate number. Slight cortical necrosis of focal distribution was present in the adrenal. The lungs demonstrated an acute pneumonitis with abscess formation from which *Streptococcus hemolyticus* was cultured. The bone marrow appeared slightly more cellular than that of the control animals. No activity was observed in the microradio-autographic studies.

Guinea pig No. 5 was given 4 mc. of radioactive gold (631.84 e.r. 4.77 r or 636.57 total r), and was sacrificed 48 hours after instillation. The only significant histologic change observed was an increased oxyphilia of the cells of the zona reticularis of the adrenal cortices. Microradio-autographs revealed a focal as well as moderately diffuse distribution of activity in the liver. The focal accumulations were observed most frequently in the midzonal areas. An occasional Kupffer cell revealed radioactivity. Some activity of focal distribution was observed in the renal glomeruli. Activity was pronounced in the lungs and assumed a focal as well as diffuse pattern and appeared to be emanating from endothelial cells of the alveolar septal capillaries. Activity was evident in the serosa of the intestinal tract and pancreatic capsule and appeared to be localized within mesothelial cells. Activity was present in the adrenals, assuming a diffuse pattern as opposed to the dense focal collections seen in all previous organs studied in this or other animals. Most activity appeared to be emanating from the endothelial cells of capillaries. One localized dense focus of activity was observed in the thyroid gland. It did not reveal any specific relationship to thyroid structure. The spleen demonstrated slight focal activity. However, the microradio-autographs were prepared 5 days after preparation of the other material due to an error in the handling of the tissue. A broad dense zone of activity was noted in the subcutaneous tissue of the skin of the abdominal wall at the site of injection.

Guinea pigs No. 6 and No. 7 received only 2 mc. of radioactive gold (425.16 e.r. +3.21 r or 428.37 total r) and were sacrificed at 49 days. The sections were essentially negative except for hypoplasia and anakmesis of gametogenic elements of the testes. There was no evidence of hepatic necrosis or extramedullary hematopoiesis. Microradio-autography failed to reveal activity.

Longevity of Radioactivity. From Table 1 the counts per second taken with the Geiger–Mueller counter over the abdominal areas of the guinea pig at 50 cm. with and without aluminum filter of 1 mm. thickness are recorded. All counts have been corrected by subtracting the background count from the total count. Although counts are observed on the 33rd day following injection, nevertheless significant activity lasts for only 12 days, coinciding with the work of Chamberlain *et al.*[3].

TABLE 1.—THE DURATION OF RADIOACTIVITY AS MEASURED AS COUNTS PER SECOND OBTAINED BY GEIGER-MUELLER COUNTER AT 50 CM. FROM THE ABDOMINAL WALL

	Guinea Pig No.						
Day of Count	*1*	*2*	*3*	*4*	*5*	*6*	*7*
After injection	3774	5457	3462	3500	5396	2429	2090
1	3749* 3520	3749* 3401	3160* 3381	2426* 3010		2000* 2349	2426* 2244
2	2795* 2799	3700* 3545	2959* 2585	2560* 2621	3453	1835* 1834	2309* 2309
5	1166* 1135	1862* 1490	1266* 1362	1220* 1161	†	677* 633	651* 639
6	693* 621	1094* 1193	998* 908	814* 573		582* 527	557* 627
7	†	732* 923	816* 779	701* 731		332* 466	443* 409
8		673* 959	686* 676	544* 535		298* 310	327* 472
9		504* 538	459* 480	350* 339		207* 228	222* 228
12		322 †	265	214		118	145
14			126	46		31	41
17			57	46		40	40
19			53	38		44	35
22			61	35		26	14
26			†	†		22	20
29						9	8
33						12	8

* with 1 mm. aluminum filter
† dead

TISSUE ACTIVITY. Table 2 reveals the counts per second in the various tissue sections cut at a thickness of 5 micra from guinea pig No. 5. This animal received 4 mc. of radioactive gold and was sacrificed in 48 hours. Significant activity is noted in the liver, spleen, and stomach in this order of decreasing magnitude. Table 2 also depicts the tissue activity of guinea pigs No. 1 and No. 2. They had received 4 mc. of radioactive gold and succumbed at 6 and 13 days, respectively. The remainder of the guinea pigs failed to reveal activity in their tissues.

THE EFFECT OF RADIOACTIVE COLLOIDAL GOLD (Au_{198}) ON WEIGHT. As shown in Table 3, loss of weight occurred in those animals receiving instillation of the radioactive material, whereas control animals demonstrated moderate gain in body weight. It was observed also that animals 1, 2, 3, and

TABLE 2.—RADIOACTIVITY OF TISSUES RECORDED AS COUNTS PER SECOND OBTAINED ON TISSUE SLICES 5 MICRONS IN THICKNESS

	Counts/Second		
Organ	*Pig No. 5*	*Pig No. 1*	*Pig No. 2*
Liver	116.3	7.9	8.6
Stomach	98.5		
Skin (inj. site)	91.0		
Spleen	60.0	5.2	4.6
Kidney	16.0		
Eye	15.3		
Lymph node	13.9		
Adrenal	13.9		
Lung	12.7	1.8	
Pancreas	12.4		
Psoas muscle	12.3		2.4
Heart	12.1		
Small intestine	11.4	1.7	
Colon	10.7		
Thyroid	10.6		
Testis	10.6		
Brain	10.5		
Bone marrow (vert.)	10.4		

TABLE 3.—EFFECT OF RADIOACTIVE GOLD (Au_{198}) ON WEIGHT OF GUINEA PIGS AT INTERVALS AFTER INSTILLATION (GM.)

	Guinea Pig No.							*Controls (C)*		
Day of Weight	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*C1*	*C2*	*C3*
Injection	334	315	332	333	480	356	356	360	343	350
6th	310*									
7th		318	359	340		374	385	377	359	361
13th		260*								
23rd			312*	284		378	421	392	379	385
26th				280*						
29th						338	419	395	388	385
49th						335	290	430	417	423

* Dead

4 appeared debilitated and showed loss of body hair before death. Although loss of body weight was noted in pigs No. 6 and No. 7, these animals remained active and showed no loss of body hair.

Discussion. According to Kelsey[11], the lethal dose of total body Roentgen irradiation for guinea pigs is 250 r. The quality of this dose was not specified. The guinea pigs used in this study received approximately 2 to 4 times Kelsey's estimated lethal dose. Those animals receiving 3 and 4 times the lethal dose succumbed within 3 weeks. However, the 2 guinea pigs that received 428 r, or slightly less than twice a supposed lethal dose of total irradiation, survived for 49 days before they were sacrificed. Weight loss was slight in one and marked in the other, although both animals were

active and did not appear debilitated as was observed in those animals succumbing to the administration of radioactive colloidal gold. The animals surviving the irradiation for 49 days revealed no essential changes in the tissues studied except for hypoplasia and anakmesis of the gametogenic elements of the testes. Conversely, 2 of the animals that died revealed focal hepatic necrosis which correlated with zones of radioactivity in the liver as depicted by microradioautography. In addition the animal which survived for only 2 weeks revealed extramedullary hematopoiesis in the liver and spleen with hypoplasia of bone marrow. These changes were noted to regress in animals surviving for 23 and 26 days. All animals that succumbed revealed hypoplasia and anakmesis of gametogenic elements of the testes.

The species differences encountered in studies of the response to total body irradiation make the clinical application of these findings difficult. Nevertheless, it has been demonstrated that following the intraperitoneal instillation of radioactive colloidal gold in large quantity, pathologic change, as well as death, similar to that encountered in total body irradiation occurs. Furthermore, at least in the guinea pig, a dose considered to be twice the lethal dose has not demonstrated any pathologic change in the tissues except in the testes of male guinea pigs. It becomes apparent that, although a wide range is available in the establishment of a therapeutic dose, nevertheless caution must be used when this agent is employed intraperitoneally, since effects of total body irradiation may be obtained.

Studies of tissue activity revealed maximum concentration in the liver, stomach,, and spleen following intraperitoneal instillation. Although the skin was noted to contain activity of similar magnitude, the only sections taken for study were from the injection site. Slight activity was observed in the kidney, eye, retroperitoneal lymph nodes, adrenal, lung, pancreas, psoas muscle, heart, small and large intestine, thyroid, téstis, brain and bone marrow. This follows the general pattern of distribution as described by Williams *et al.*[18], in rats and mice.

Microradio-autographs revealed the pattern of activity in all tissues except the adrenal to be characterized by dense focal aggregates. This type of distribution has been explained by Hahn[6], who believes that radioactive colloidal atoms occur as aggregates on an inert nidus of tissue due to pH changes and the duration of time the colloidal material is retained in the tissue. For the most part radioactive colloidal gold was most abundant in tissue containing large quantities of reticuloendothelial cells. The Kupffer cells of the liver, endothelial cells of the septal capillaries of the lung, adrenal vessels, renal glomeruli, the mesothelial cells of the serosa of the gastrointestinal tract, and the pancreatic capsule all demonstrated localization of activity. Yet in many instances no localization as to cell distribution could be determined. Furthermore, in sections revealing activity localized to a specific cell type, it was observed that many of these cells in any given zone were free of activity.

Summary. The instillation of radioactive colloidal gold (Au_{198}) intraperitoneally in guinea pigs produced effects similar to those of total body irradiation. There was loss of body weight and hair in all animals receiving this substance. Guinea pigs receiving approximately 3 to 4 times the lethal dose of radioactive colloidal gold succumbed 3 weeks after instillation. The outstanding morphologic

changes were focal hepatic necrosis, hypoplasia of bone marrow, myeloid metaplasia of liver and spleen, and atrophy of testes. Animals receiving twice the lethal dose sacrificed 49 days after instillation of radioactive colloidal gold demonstrated hypoplasia and anakmesis of testes.

The maximum concentration of radioactive colloidal gold was observed in liver, stomach, and spleen, although all other organs and tissues revealed activity of minimal degree after intraperitoneal instillation. Radioactivity was distributed in the tissues chiefly in a focal manner.

We are indebted to Dr. Otto Glasser for his valuable advice in this study and the technical assistance of Mrs. Elizabeth Haskell and Mr. Bernard Tautkins.

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FLUID, ELECTROLYTE, AND PROTEIN DEPLETION SECONDARY TO THE BRONCHORRHEA OF PULMONARY ADENOMATOSIS: A COMPLICATION HERETOFORE UNREPORTED

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It is well recognized that severe, and often fatal, fluid and electrolyte depletion can result from protracted vomiting and diarrheal states, pyloric and intestinal obstruction, draining fistulae, continued gastric and intestinal intubation-suction and other mechanisms causing excessive loss of essential body fluids. To our knowledge, there has been no previously recorded instance of such a state of depletion produced by the loss of bronchial secretions. The following case of pulmonary adenomatosis manifests these alterations as shown by the clinical picture, by volumetric and chemical determinations of fluid, protein, and electrolyte loss through the bronchial route, by an altered fluid balance, and by a rapid clinical improvement following replacement therapy.

Case Report. A 65-year old white male, Jewish broker, was referred to the Chevalier Jackson Clinic of Broncho-Esophagology on January 24, 1950, with a diagnosis of "stricture of the lower end of the esophagus, with possible fistulous tract to the bronchus".

The patient had noted difficulty in swallowing for over 20 years. The rapid swallowing of foods and particularly cold liquids would result in a sensation of constriction at a point localized behind the lower end of the sternum, but never with regurgitation. This was not distressing enough to require medical attention until the summer of 1949. At this time a "wet spot" was found in his lungs by a physician who advised a roentgenogram, believing that his esophagus was responsible for the "wet spot" by "backing up". Endoscopy was suggested, so the patient entered a hospital where he was told he had an esophageal stricture. A series of 4 dilatations was performed, about a month apart, the last on December 5, 1949.

During the past year the patient had noted an increasing tendency to cough, with the oral evacuation of fluid and with vague pain in various parts of the body, chiefly in the back and legs. The cough was productive of copious amounts of thin watery material with no admixture of anything recognizable. The evacuation of this fluid was facilitated by lying on his left side, when as much as 8 to 10 ounces of thin, slightly opalescent watery material would be raised within a few minutes. His weight, which had been constant, had dropped 15 pounds in the past 6 months. Mild dyspnea on exertion had been noted recently. There had been no hemoptysis, hoarseness, chest pain, or night sweats. The past medical, social, and family histories as well as systemic inquiry were not significant.

Physical examination revealed a well developed adult white male of fair nutrition, who appeared chronically ill. There was no cyanosis, venous distention, or clubbing of the fingers. The temperature was 98.6° F., the pulse 80, respiratory rate 28, and the blood pressure 110/70. The cardiac examination revealed normal findings. The chest was emphysematous, with dullness and increased fremitus over almost the entire left lower hemithorax and dullness at the extreme base of the right chest. Distinct tubular breathing and a few moist râles were audible at the left base, and bronchovesicular breath sounds with numerous coarse and

fine râles at the right base. After coughing and expectoration of about 200 cc. of thin watery fluid, aeration of both bases improved greatly with fewer râles but with no alteration in the tubular quality of the breath sounds at the left base. The remainder of the physical examination was not remarkable.

Laboratory studies on admission revealed a hemoglobin of 17.4 gm., red cells 6.13 million, leukocytes 16,700, with neutrophils as well as intake-output and daily weight records.

Extensive Roentgen studies of the chest (Fig. 1) revealed: "Abnormal mottled and confluent density in the lower portions of both lungs. This is moderately extensive in the lower third of the right lung and is quite pronounced in the lower half of the left lung. On the left side the density is largely confluent or homogeneous, and through this density the negative shadows of the air-containing bronchial branches of the left lower lobe are well visualized." An exhaustive study was made of the esophagus on the presumption that the extensive lung disease was on the basis of aspiration pneumonitis, but there was: "No evidence of spill-over of barium into the glottis, nor have we found any evidence of esophageal perforation or esophago-tracheal or esophago-bronchial fistula. However, a definite constricting lesion is demonstrated at the lower end of the esoph-

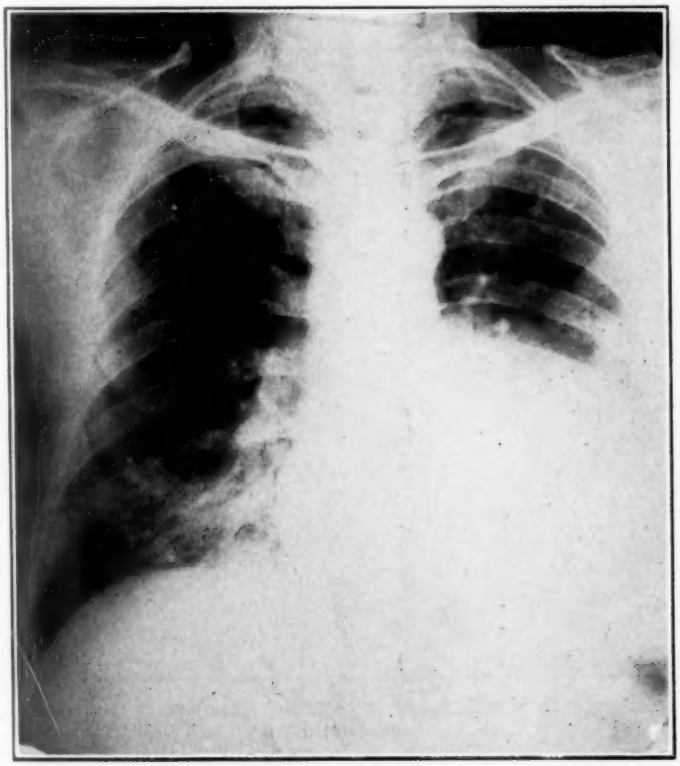

FIG. 1.—Roentgenogram on Jan. 26, 1950, of patient with pulmonary adenomatosis.

80%, lymphocytes 17%, monocytes 2%, and eosinophils 1%. The urine had a specific gravity of 1.017 and was normal. The fasting blood sugar was elevated: 188 mg. per 100 cc., and the blood urea nitrogen was quite high: 100 mg. The Kolmer and Kahn reactions were negative.

CLINICAL COURSE. The patient remained afebrile for his entire hospital stay. Shortly after admission careful tabulations were kept of the amount of expectorate produced daily,

agus: this is not typical of chronic cardiospasm, inasmuch as the esophagus shows no unusual dilatation; it is not typical of a neoplastic process."

The bronchoscopist reported: "Tracheobronchial tree inspected and found grossly normal except for a large amount of very thin bronchial secretion." Esophagoscopic examination showed: "A moderate amount of fluid aspirated but no stasis of solid material encountered. The scope passed through into the stomach with little resistance. The mucous membrane in the region of the esophagogastric junction showed slight congestion." The patient received 2 esophageal dilatations with moderate improvement in the dysphagia.

Because of the abnormal fasting blood sugar, a glucose tolerance test was performed which revealed a mild diabetes mellitus. Subsequent blood and urine sugar determinations were within normal range on a dietary regimen alone.

By February 8, 1950, after adequate fluid and dietary intake, the blood urea nitrogen had dropped to 14 mg. per 100 cc. The expectorated material was tested for the presence of gastric content with negative findings. The pH was 8.0 and no pepsin was detected. A fractional gastric analysis showed normal acid values. Because of the remote possibility of a renal-bronchial fistulous connection, urea determinations of the expectorate and urine were done. The former gave a value of 46.5 mg. per 100 cc., whereas the latter showed 1450 mg. per 100 cc. Skin tests with histoplasmin, blastomycin, and coccidioidin were negative. The Mantoux test (P.P.D.) was positive in the first dilution.

Many specimens of the expectorate were examined and cultured for acid-fast bacilli and fungi, with consistently negative results. Aerobic and anaerobic bacterial cultures disclosed moderate numbers of *N. flava*, *N. sicca*, *N. catarrhalis*, viridans hemolytic streptococci (not group A), and non-hemolytic streptococci, all of which were sensitive to either penicillin or streptomycin.

Cytologic study of the bronchial washings (Fig. 2) was reported: "Class 3, suspicious of malignancy. Is there a possibility of this being pulmonary adenomatosis?" A smear for cellular elements showed: "rare eosinophil; many cells which resemble plasma cells."

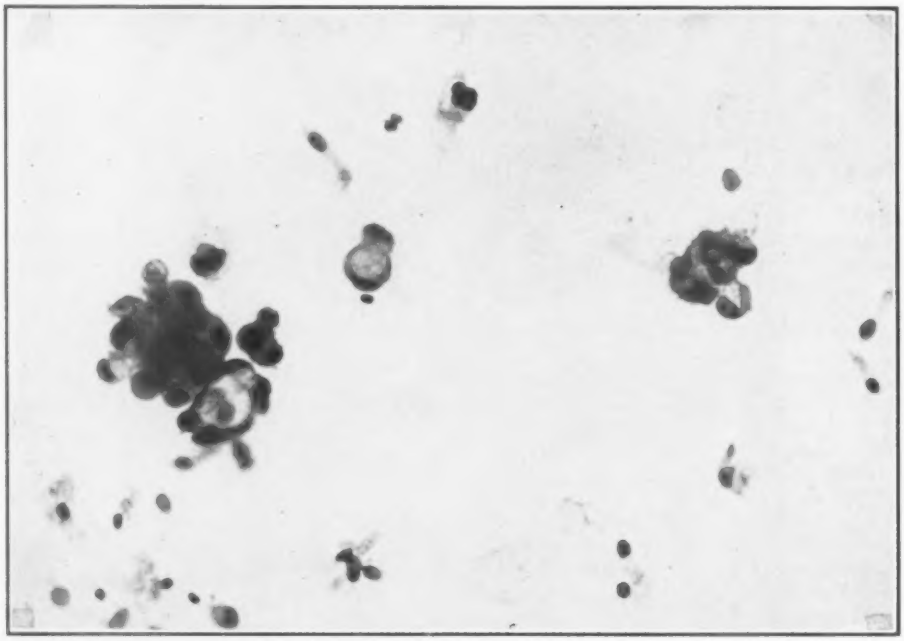

FIG. 2.—Photomicrograph of cells found in bronchial secretions of patient with pulmonary adenomatosis.

Because of lack of definitive diagnosis, a needle aspiration biopsy of the left lower lung was performed (Fig. 3). This was reported: "The specimen contains papillary structures sectioned in various planes. The lining cells are slightly obscure but they can be seen as cylindrical elements with a tendency to vacuolization of the cytoplasm and nuclei which are quite regular; the cells are similar to those seen on bronchial smear. Diagnosis: Papillary adenomatosis."

The Trousseau and Chvostek signs were negative. Electrocardiographic study showed a sinus tachycardia, P-R interval .20 sec., and abnormally low QRS complexes with comparatively high T-waves.

Correlative examinations of expectorate, blood, and urine were made on March 21, 1950, and on several subsequent dates (Table 1). Fluid balance studies performed on March 23, 1950, disclosed significant deficits in the body fluids, proteins and electrolytes (Table 2). The low chloride figure (291 mg.) on March 21st is the more significant in view of the then existing hemoconcentration indicated by the high red cell count (6.1 million) and the high blood protein (8.1 gm.). An intensive program of both parenteral and oral fluid, electrolyte and protein supplementation was begun on March 21, 1950, in an effort to correct the obvious deficiencies. The treatment consisted in the intravenous administration of 1000 cc. of Darrow's solution, 1000 cc. of 10% glucose in water solution, and 10 cc. of calcium gluconate solution. The following day he was given 1000 cc. of 5% glucose in saline solution and 1000 cc. of amigen (R) solution intravenously. The oral

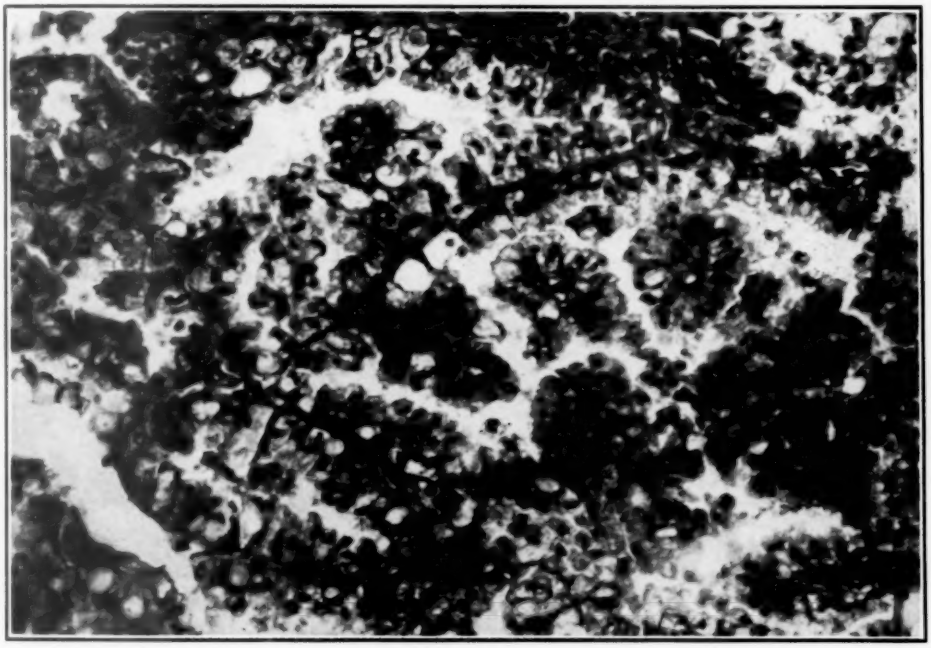

FIG. 3.—Photomicrograph of specimen obtained by aspiration needle biopsy in patient with pulmonary adenomatosis.

The patient continued to bring up copious quantities of thin watery material (Fig. 4) and on many days this far exceeded the urinary output. On March 18, 1950, the expectorate totaled almost 2 liters for a 24-hour period. Just prior to this the patient began to complain of severe muscular cramps, most marked in the calves and feet. In addition there was general malaise, lassitude, loss of appetite, and moderate generalized weakness. He was now content to lie in bed most of the day, whereas previously he had been ambulant. The deep tendon reflexes became hypoactive and the blood pressure dropped to 88/60. The pulse rate ranged from 100 to 110. The heart tones were of poor quality.

intake of fluid was encouraged to tolerance. In addition to a high protein diet, the patient received 4 cc. of concentrated meat extract (mainly for the high potassium content) 4 times daily, 15 to 30 gm. of skim milk powder in milk 3 times a day, 15 micrograms of B_{12} parenterally daily, large quantities of oral and parenteral multivitamins, and frequent feedings of soups and beef broths containing large amounts of added salt.

veal any alterations on comparison with previous studies. The general condition of the patient continued to improve, the blood chemical studies showed a return to normal values, and on April 25th the patient was discharged.

He was re-admitted for further study on May 31, 1950. He stated he felt well and presented no new complaints or symptoms. During the interval at home his daily volume

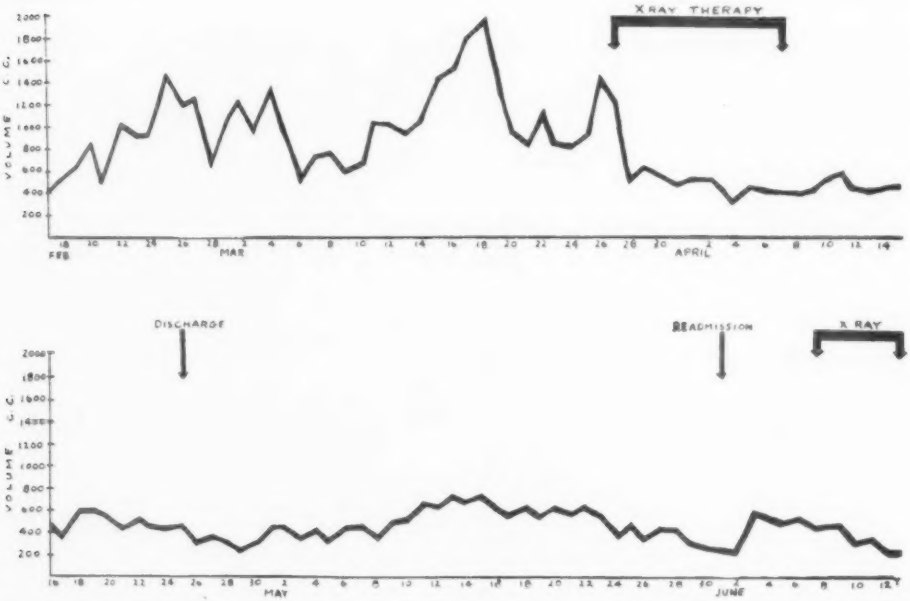

FIG. 4.—Record of daily output of bronchial secretion between Feb. 18 and June 12, 1950, in a patient with pulmonary adenomatosis.

This produced an almost immediate improvement in the patient's general condition. Within a few days after the onset of the corrective therapy he regained his appetite, the severe cramps were relieved, his strength improved dramatically, and he once again became active and ambulant. There was transient mild pitting ankle edema during this treatment period, but it soon receded and was never again evident.

Because of the gravity of the patient's clinical condition, Roentgen-ray therapy to the left chest was begun on March 28, 1950. As shown in Fig. 4, this was followed by a significant drop in the daily amount of expectorated material. The patient received a dosage of 2000 roentgens (air). Subsequent Roentgen studies of the chest failed to re-

of expectorate had ranged from 270 cc. to an unusual 800 cc. (Fig. 4). Urinalysis was negative, the hemoglobin 13.8 gm., red cells 5.1 million, leukocytes 13,700, with 78% neutrophils, 15% lymphocytes, 1% monocytes, and 8% eosinophils. The fasting blood sugar was 121 mg. per 100 cc. The blood pressure was 110/70, and the other physical findings were essentially the same as previously noted.

A series of re-examinations was carried out that showed no material change from previous observations.

The roentgenographic studies of the chest showed no significant difference from the findings noted over a period of 4 months.

Bronchoscopy revealed: "Moderate amounts of thin fluid, having the appearance of saliva, are encountered in the trachea and left bron-

chial tree. A total of 1 ounce was aspirated. There is much less fluid on the right side. The mucosa shows no particular inflammatory change."

Cytologic examination of the aspirated material gave findings similar to those on the previous study.

Chemical analysis of the expectorate again revealed significant losses of protein and electrolytes by this route (Table 1).

The patient was discharged on June 15, 1950, in better condition generally than at any time in the 12 months before. He was readmitted to the hospital on November 15, 1950, for follow-up study, and he stated that he felt well and presented no new symptoms. In the preceding 5 months careful daily tabulations of the sputum volume had again been recorded. The volume in this interval averaged about 200 cc. (6.75 oz.) daily.

TABLE 1.—ANALYTICAL DATA OF EXPECTORATE, BLOOD AND URINE IN A PATIENT WITH EXCESSIVE BRONCHORRHEA DUE TO PULMONARY ADENOMATOSIS

	Expectorate			*Blood*				*Urine*
Date	3/21/50	3/27/50	6/5/50	3/21/50	3/27/50	4/20/50	6/3/50	3/27/50
Volume (cc.)	1220	1200	500					
Chlorides (mg. per 100 cc.)	392	410	366	291		361	384	367
Sodium (mEq/L.)	144	144	134		141	146		190
Calcium (mg. per 100 cc.)	8.2	6.3	8.5	9.4	7.7	9.9	9.6	9.6
Potassium (mEq/L.)	6.85	6.4	7.6	5.95	5		4.93	52.5
Urea Nitrogen (mg. per 100 cc.)	90		55	80		15	16	
Sugar (mg. per 100 cc.)	77		55					
Total Proteins (gm. per 100 cc.)	4.5(?)	.269	1.1	8.1	5.3	7.2	5.8	
Albumin (gm. per 100 cc.)		.055	.9	4.5	3.2	5.0	4.5	
Globulin (gm. per 100 cc.)		.244	.2	3.6	2.1	2.2	1.3	
CO_2 (Vol.%)				39				
Hematocrit				65%	42%		43%	

Guinea pigs were sacrificed that had been injected 4 months previously (March 18, 1950) with fluid aspirated at bronchoscopy. The animals showed no evidence of adenomatosis. This procedure was suggested by the work of Norris[10], who observed a picture similar to adenomatosis in a guinea pig injected with a pleural fluid from a patient with lobar pneumonia. More recently, Good *et al.*[5] have also reported negative results in animal inoculation studies.

Because of the apparent benefit derived from the first course of Roentgen-ray therapy, a second course of treatment (a total dose of 1200 roentgens in air) was given to the left chest. During this period there was a further decline in the quantity of expectorate to the lowest levels yet noted (Fig. 4). No treatment was given at any time to the right chest, lest there result a serious degree of bilateral pulmonary fibrosis.

No significant changes were noted on physical examination. Bronchoscopic, bacteriologic, and complete Roentgen studies of the chest failed to disclose any appreciable changes from those previously observed. The hemogram was within normal limits and the urine revealed a moderate amount of albumin.

Amylase activity was determined on the patient's serum (26 gluc. equiv.), saliva (102,500 and 130,000 gluc. equiv.) and expectorate (42,000 and 66,500 gluc. equiv.). The saliva of 4 normal controls showed an average amylase activity of 24,700 gluc. equiv. Further Roentgen therapy was deferred because of the favorable course of the patient's illness. He was discharged on November 21, 1950, on a high protein diet with vitamin and electrolyte supplements.

The patient was again admitted to the hospital on April 1, 1951, for re-evaluation.

His nutrition and strength were improved; however, he continued to complain of easy fatigue and dyspnea on slight exertion. His weight was 162 pounds and his average daily sputum volume ranged from 300 to 600 cc. The physical findings were essentially the same as previously noted. Laboratory studies disclosed a hemoglobin of 15.3 gm., a transient trace of glycosuria, and bacteriologic and cytologic findings of the bronchial secretions similar to the earlier ones. The blood sugar was 131 mg. The serum electrolytes were within normal range and the serum proteins were 6.7 gm. per 100 cc., with an A/G ratio of 1 to 1.2. The chest roentgenogram revealed more consolidation and increased density in the involved areas, denoting some progression of the disease.

Because of this progression and some increase in sputum volume, the use of nitrogen mustard therapy was considered. This agent is radiomimetic and it is known that a large fraction of the intravenous dose is either absorbed or inactivated in the lung. Accordingly, on April 6, 1951, a 20-mg. intravenous dose was given to the patient without incident. The patient was discharged on April 8, 1951, in an unchanged condition and was to return for follow-up treatment.

On May 29, 1951, the patient once again entered the hospital. The sputum volume had increased to 1000 to 1200 cc. daily, and the dyspnea had increased to such an extent that even mild exertion, such as combing the hair or slowly walking down the corridor, would at times cause considerable respiratory distress. In this 2-month interval, the physical and Roentgen findings revealed a moderate progression of the abnormal changes in the lower lung fields. The abnormal densities appeared more compact, but the extent of the disease remained about the same. The significant laboratory findings included a serum chloride of 362 mg. per 100 cc., a serum sodium of 120 mEq/L., and a serum potassium of 5.35 mEq/L. The hemogram, serum proteins, urine, and other studies, including bronchoscopy and bronchial secretion studies, were essentially the same as previously noted. The circulation time (saccharine) was 28 seconds; the ether time could not be determined. The patient was given large doses of Banthine® a quaternary ammonium parasympathetic blocking agent, with no effect noted on the daily sputum volume. Digitoxin was given in full dosage with a resultant 7-pound weight loss but with no apparent benefit in the subjective dyspnea. Because of the progression of the disease and the probable previous benefit derived from Roentgen treatment, the patient was given another course of therapy. From June 5 to June 13, 1951, he received a total of 1600 roentgens (in air) to the right anterior chest. On June 14, 1951, the patient was discharged on digitoxin, protein, and electrolyte supplements and oral vitamins. His general condition was unchanged.

On September 25, 1951, the patient was subsequently admitted to the service of Dr. Benjamin Burbank at the Long Island College Hospital. The findings at this time were almost similar to those noted previously and there were no appreciable changes in serial roentgenographic studies. There had been a slight regression in his general condition and treatment continued to be purely symptomatic. The sputum volume had decreased from 20 to 8 ounces a day. In the early hours of October 11, 1951, he suddenly cried out with severe substernal pain and expired almost immediately. Permission for necropsy was not granted.

Discussion. Pulmonary adenomatosis is a rare disease of late or middle life. To date almost 100 cases[14,19,20] have been reported in the literature, but in only 6 of these[1,2,6,20-22] had the diagnosis been established ante mortem when we so diagnosed our patient. Since then, an additional 14 have been so recognized[5,9,11,15]. From a pathological standpoint, the disease had been compared to the infectious pulmonary disease of sheep known as jagziekte[7,22]. Although the two are morphologically similar, the infectious nature of the human disease has never been proven. The pathological, roentgenographic, and clinical aspects of the disease have been extensively reviewed by several writers[4,8,19,21,22].

The clinical features which should arouse a suspicion of the disease are cough and the expectoration of copious quantities of non-odorous clear, watery, frothy "sputum". Dyspnea, weight loss, and weakness are common. Fever, hemoptysis, anemia, and leukocytosis are usually absent[21]. These findings, along with multicentric pulmonary densities clinically and roentgenographically and the failure to discover

a primary site for metastatic malignant growths in the lungs, should suggest the diagnosis.

In this patient, our first thought was that the pulmonary disease represented an aspiration pneumonitis, or so-called "drowned lung." This we believed to be due to an esophageal stricture with overflow and secondary spill into the tracheobronchial tree. Detailed roentgenographic and endoscopic studies failed to substantiate this original impression. The cytologic study of the bronchial secretions (Fig. 2), although non-specific, hinted at the proper diagnosis. A needle aspiration biopsy (Fig. 3) of the left lung revealed the typical histopathology of pulmonary adenomatosis. The procedure of needle biopsy is used in this hospital with considerable success[16], and in this instance established the diagnosis. In 3 other cases[9,18,21] of this type it was also of value in establishing the diagnosis.

One of the most interesting aspects of this disease, and exemplified in this particular case, is the voluminous quantity of bronchial secretion produced over a long period. In less than 4 months, our patient spat up about 78.2 liters of expectorate. This far exceeded his body weight (67.1 Kg.), and amounted to some 20 gallons of fluid, or a daily average of about 650 cc. In one 24-hour period, there were almost 2000 cc. of secretion, and on many days the expectorated fluid exceeded the urinary output.

In addition to the large depletion of fluid, considerable losses of electrolytes and other body stores occurred. It is estimated that in this period of observation (120 days) the patient lost, through the bronchial route, about 780 gm. of protein and about 470 gm. (over 1 pound) of sodium chloride. The losses of calcium, potassium, glucose, and other undetermined substances are also significant when considered over such a long period. The fluid balance studies (Table 2) showed that the plasma volume was the only part of the body fluids which was reduced. This amounted to about 50% of normal values. The extracellular fluid was hypotonic because salt was lost in excess of water and one could therefore assume that there had been some slight increase in the intracellular fluid volume. There was no appreciable reduction in the red cell volume, perhaps in part because of hemoconcentration, in part because the pulmonary disease was stimulus to red cell production. No apparent deficiency of potassium was noted, but this did not exclude intracellular potassium loss.

On the basis of these studies, it was estimated that the patient needed (in addition to daily requirements) about 1500 cc. of water, 20 gm. of sodium chloride, and approximately 1000 gm. of protein. The details of dosage and mode of administration have been stated. The severe muscle cramps, lassitude, weakness, hyporeflexia, hypotension, poor appetite, and general debility, as well as the hemoconcentration and abnormal blood chemical values (Table 1) improved dramatically within a few days after the institution of this parenteral and oral corrective-replacement therapy.

The unusual degree of amylase activity demonstrated in the expectorate of this patient is unexplained. Whether the products of the glandular elements of this tumor possess high amylase activity, or whether this merely represents an admixture of saliva during the process of expectoration, is not clear; however, the latter appears unlikely. Further studies on the amylase activity of the saliva of other subjects are being pursued at the present time.

Surgical extirpation of the involved pulmonary segments[1,14,15] is the only

method of curative treatment for this disease. However, in our patient the extent and bilateral distribution of the lesions precluded any such procedure. Roentgen therapy, although unsuccessful when tried in other reported cases, was the only alternative. Although producing no regression demonstrable in roentgenographic films, this therapy was followed by a significant drop in the daily volume of expectorate (Fig. 4), and encouraged us to use the treatment a second time. Whereas the average amount of expectorate before the beginning of therapy was about 1020 cc. per day, it fell to about 470 cc. per day after the first course of Roentgen-ray therapy, and less than 300 cc. per day at the end of the second course.

Nitrogen mustard therapy was without benefit in our patient and a similar failure was reported in 2 other cases[5,9].

The mechanism of the loss of fluid and electrolytes may be speculated upon. The possibilities include: 1) a simple filtration of water and small molecular substances from an extensive tumor in direct connection with alveolar spaces; 2) a secretion of these substances by such a tumor with a glandular structure; 3) an inflammatory exudate from such a tumor. The latter seems least contributory because of the relatively lower protein content of the expectorate and lesser depletion of blood proteins. A single observation of a total protein of 4.5 gm. per 100 cc. of expectorate could not be confirmed, and, we suspect, was probably in error. The concentrations of the several electrolytes were approximately those obtaining at the time in the blood, except in the case of the first 2 observations on chlorides in the expectorate, which gave values dis-

TABLE 2.—FLUID BALANCE STUDIES ON MARCH 23, 1950, IN A PATIENT WITH BRONCHORRHEA DUE TO PULMONARY ADENOMATOSIS

		Normal values calculated for patient's present and usual weights	
	Observed values in patient	*For 67.1 K. (present wt.)*	*For 72.7 K. (usual wt.)*
* Total extracellular fluid (SCN Space)	12,700 cc.	12,900 cc.	14,000 cc.
Interstitial fluid	11,200 cc.	10,000 cc.	10,900 cc.
† Plasma volume	1,555 cc.	2,900 cc.	3,100 cc.
Red cell volume	2,335 cc.	2,300 cc.	3,100 cc.
	(Hematocrit 60%)	(Hematocrit 45%)	
Total blood volume	3,890 cc.	5,200 cc.	5,600 cc.
Total protein in plasma	139 gm.	174 gm.	186 gm.
Protein loss in serum or plasma		35 gm.	47 gm.
‡ Total body protein loss		1,050 gm.	1,410 gm.
Total plasma chlorides	4,040 mg.	10,400 mg.	11,200 mg.
Total extracellular chlorides	34,200 mg.	46,500 mg.	50,500 mg.
Chloride deficit		12,300 mg.	16,500 mg.
Total plasma potassium	86.5 mEq/L.	14.5 mEq/L.	15.5 mEq/L.
Total extracellular potassium	71.2 mEq/L.	64.5 mEq/L.	70.0 mEq/L.

* Normals calculated on basis of interstitial fluid forming 15% of body weight and normal hematocrit being 45.

† Method of Evan's Blue (T-1824).

‡ (Elman) 30 gm. body protein lost for every gram lost in blood plasma.

tinctly higher than those in the blood and, on one occasion, in the urine. The possibility of some secretory activity as well as simple filtration must be admitted. There is nothing to suggest a nervous mechanism, such as may have been active in the salt-wasting syndrome associated with cerebral disease (meningitis) reported by Peters *et al.*[13] and seen by us in similar cases (to be published).

Summary. 1 There is reported the twenty-first case of pulmonary adenomatosis in which the diagnosis was established ante mortem.

2. Cytologic study of the bronchial secretions suggested the diagnosis.

3. Needle aspiration biopsy established the diagnosis.

4. This is the first recorded instance of a bronchorrhea of such extreme degree that it resulted in fluid, electrolyte, and protein depletion.

5. Data on fluid balance and chemical analyses of expectorate and blood before and after successful replacement therapy are presented.

6. Roentgen ray treatment twice resulted in temporary but appreciable clinical improvement.

7. Nitrogen mustard therapy gave no improvement.

8. Injection of bronchial secretion into guinea pigs produced no lesions.

We acknowledge our debt to Dr. Chevalier L. Jackson for permission to study this patient, and to Dr. Joan H. Long, who performed the fluid balance studies.

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A COMPARISON OF PRECORDIAL ELECTROCARDIOGRAMS USING INDIFFERENT ELECTRODES V, CR, AND RS

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Through the use of unipolar electrocardiograms, many errors of interpretation have been avoided which were commonly encountered with the bipolar leads. Diagnostic possibilities have increased but no unanimity of opinion exists in regard to which indifferent electrode shall be recommended for routine use. The left leg (CF), formerly popularly used as the indifferent electrode, has now been abandoned on theoretical as well as practical grounds, since it has been known that potential variations of the left leg influence the semidirect precordial leads[1-4]. For all practical purposes the small potentials of the Wilson central terminal (V) would seem to answer most objections, but its use, too, has been questioned by Wolferth[12-15], who recommends the area over the spine of the right scapula (RS). Myers[8] has shown that potential variations of the heart may be followed to the extremities and that a similarity exists between the area of the right scapula and the right arm. If this is true, then the predominantly negative potentials found in the right arm and over the right scapula should increase the positivity of the deflections of the CR and RS precordial leads as compared to the V leads. In addition the semi-direct CR and RS leads should be similar in appearance.

The American Heart Association[9] was unable to recommend an indifferent electrode for routine use. Therefore, it was thought worth while to compare the following electrocardiograms employing, as indifferent electrodes, V, CR, and RS to determine if differences were present and, if so, their significance.

Method. For this purpose electrocardiograms on 98 unselected ambulant patients from the Oak Forest Infirmary were studied. The tracings were all obtained in the supine position, the leads being: Standard leads I, II, III; augmented unipolar limb leads aV_L, aV_F, aV_R; precordial leads V_1 through V_7, CR_1 through CR_7 and RS_1 through RS_7. The same chest positions were used for each indifferent electrode. All the measurements made were corrected for errors in standardization.

The measurements and directions of the P, QRS, and T waves in lead aV_R were made, providing the right arm potentials. Similarly the measurements and directions of the P, QRS, and T waves and the positions of the transition zone were recorded for the precordial leads. Thus a comparison was pos-

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sible between the so-called indifferent electrodes. The tracings were divided into normal and abnormal groups, which, in the case of the precordial leads, were based upon the criteria established by Wilson and Myers[7,10].

Results. Table 1 shows the measurements of the QRS complex in aV_R expressed as the algebraic sum of the total upward and downward deflections for normal and abnormal cases. In 88% of the normal group and 58% of the abnormal group the amplitude of the QRS deflections is minus 4 mm. or deeper. No positive QRS deflections were encountered in the normal groups and only two were found in the abnormal groups. Since aV_R is an augmented lead, these figures are 50% greater than the actual potential variations of the right arm.

The location of the transition zone is indicated in Table 2. In the normal group the transition zone in the V leads ranges between chest position 2 and 4 to 5. In all but one the transition zone ranges between chest position 1 to 2 and 4 in the CR and RS leads. Among the abnormal cases the variation of the position of the transition zone between the 3 indifferent electrodes is not so apparent, but the similarity between the CR and RS leads is striking. If the normal and abnormal groups are added together, the transi-

TABLE 1.—MEASUREMENTS OF THE QRS COMPLEX aV_R IN NORMAL AND ABNORMAL CASES

Normals

Average amplitude in mm.	−12	−11−10	−9−8	−7−6	−5−4	−3−2	−1−0	+1+2	+3+4
Number of cases	4	2	8	11	19	4	2	—	—

Abnormals

Average amplitude in mm.	−18	−15	−11−10	−9−8	−7−6	−5−4	−3−2	−1−0	+1+2	+3+4
Number of cases	1	1	1	5	8	12	12	6	1	1

TABLE 2.—SHOWING POSITION OF THE TRANSITION ZONE FOR NORMAL AND ABNORMAL CASES

Normal

	1−2	*2*	*2−3*	*3*	*3−4*	*4*	*4−5*
V	—	4	13	10	18	1	4
CR	3	12	13	9	12	1	—
RS	3	12	12	10	11	1	1

Abnormal

	1	*1−2*	*2*	*2−3*	*3*	*3−4*	*4*	*4−5*	*5*	*5−6*	*6*
V	1	1	1	2	9	17	5	10	1	1	—
CR	1	3	1	4	11	15	6	5	1	—	1
RS	1	3	1	2	11	17	5	6	1	—	1

tion zone in the V leads in 91% of the cases ranges between chest positions 2 to 3 and 4 to 5. However, in 92% of the CR leads and 90% of the RS leads the transition zone falls between position 1 to 2 and 4.

The configuration of the P waves is illustrated in Table 3. In 78% of the cases in the normal group the P wave in V_1 is either inverted or diphasic, whereas in CR_1 and RS_1 the P waves are either isoelectric or upright in 84 and 80% of the cases, respectively. Excluding 6 cases of auricular fibrillation, a similar tendency toward greater positivity of the P wave in CR_1 and RS_1 is shown in the abnormal group. In 96% of the normal and 90% of the abnormal cases the P wave in aV_R is inverted. No differences in the direction of the P waves were encountered over the left precordium, but a general tendency toward greater positivity of CR and RS leads was evident.

Table 4 shows a comparison of the R waves and S waves (V, CR, and RS) from chest positions 1 and 2 of the normal group. For this comparison a difference of more than 2 mm. existed before it was considered significant. In V_1 the R wave was lower than in CR_1 or RS_1 in 8 of 50 cases. In 42 of 50 cases the R waves in V_1, CR_1, and RS_1 were equal. Several tracings disclosed a QS complex at chest position 1 for all 3 indifferent electrodes. These were recorded as equals under the R wave classification. Ordinarily at chest position 1, the R waves are of such low amplitudes that precise measurements are prevented. Accordingly the S wave measurements are com-

TABLE 3.—TYPES OF P WAVES AMONG NORMAL AND ABNORMAL CASES

NOTE: Technically poor aV_R in 1 normal case prevented P wave measurements

	Normal				*Abnormal*			
P Waves	V_1	CR_1	RS_1	aV_R	V_1	CR_1	RS_1	aV_R
Inverted	17	2	3	47	16	3	2	38
Diphasic	22	6	7	—	17	11	13	—
Isoelectric	6	10	6	2	6	7	9	2
Upright	5	32	34	—	3	21	18	2

TABLE 4.—COMPARISON OF QRS COMPLEXES FROM THE RIGHT PRECORDIUM IN NORMAL CASES

CHEST POSITION 1

R Waves		*S Waves*	
V < CR = RS	8 cases	V > CR = RS	35 cases
V = CR = RS	42 cases	V = CR = RS	15 cases

CHEST POSITION 2

R Waves		*S Waves*	
V < CR = RS	26 cases	V > CR = RS	21 cases
V = CR = RS	24 cases	V = CR = RS	29 cases

pared. In V_1 the S wave was deeper than in CR_1 or RS_1 in 35 of 50 cases. The S wave was of equal depth in V_1, CR_1, and RS_1 in 15 of 50 cases.

At V_2 (Table 4) the R wave was smaller than in CR_2 or RS_2 in 26 of 50 cases and all were equal in 24 of 50 cases. The S wave at V_2 was deeper than at CR_2 or RS_2 in 21 and equal in 29 of the 50 cases. In all these normal cases the R and S waves were equal in comparable CR and RS leads.

At V_2 (Table 5) the R wave was lower than in CR_2 or RS_2 in 9 of the 47 cases while in 37 of 48 cases all were equal. One case exhibited a taller R wave in CR_2 than in either V_2 or RS_2. Another case disclosed a smaller R wave in RS_2 than in V_2 or CR_2, the latter being of equal amplitude. The S wave in V_2 was deeper than in CR_2 or RS_2 in 21 of 48 cases, and in 20 cases all were equal. Seven cases revealed a deeper S in CR_2 and RS_2 than

TABLE 5.—COMPARISON OF QRS COMPLEXES FROM THE RIGHT PRECORDIUM IN ABNORMAL CASES

CHEST POSITION 1

R Waves		*S Waves*	
V < CR = RS	5 cases	V > CR = RS	22 cases
V > CR = RS	2 cases	V = CR = RS	21 cases
RS > CR = V	1 case	V < CR = RS	4 cases
V = CR = RS	40 cases	CR < V = RS	1 case

CHEST POSITION 2

R Waves		*S Waves*	
V < CR = RS	9 cases	V > CR = RS	21 cases
V = CR = RS	37 cases	V = CR = RS	20 cases
CR > V = RS	1 case	V < CR = RS	7 cases
RS < V = CR	1 case		

Table 5 represents a comparison of the QRS complexes from the right precordium of the group classified as abnormal. In V_1 the R wave was smaller than in CR_1 or RS_1 in 5, taller in 2 and equal in 40 of the 48 cases. In 1 instance the R wave in RS_1 was taller than in CR_1 or V_1, the latter being equal. The S wave in V_1 was deeper than CR_1 or RS_1 in 22, less deep in 4, and equal in 21 of the 48 cases. One case showed a smaller S wave in CR_1 than in V_1 or RS_1, the latter being equal.

in V_2, the former being equal. The QS complex at the C_1 or C_2 position was classified as in the normal group. The presence of a Q wave in 1 lead and not in another is described in detail later.

Comparisons of the R waves from the left precordium in the normal and abnormal groups are recorded in Table 6. Since the S waves corresponded so closely to the R differences, or were frequently absent, they are not tabulated. In 34 of 50 normal cases the R wave at V_5 and V_6 was lower

than that in $CR_{5,6}$ and $RS_{5,6}$ while in 14 cases all were of equal amplitude. In 2 cases the R wave in $CR_{5,6}$ was taller than that of $V_{5,6}$, or $RS_{5,6}$, the latter being equal. In 32 of 47 cases of the abnormal group the R wave in $V_{5,6}$ was smaller than in $CR_{5,6}$ and $RS_{5,6}$, while in 13 cases all were equal.

waves in V_1 were inverted or diphasic in 25 of 50 cases, while in CR_1 and RS_1 the T waves were isoelectric or upright in 48 of 50 cases. At chest position 2 upright T waves were displayed in 46, 49, and 48 of 50 cases for V_2, CR_2, and RS_2 leads, respectively. Similar high percentages for upright T waves

TABLE 6.—COMPARISON OF R WAVE FROM THE LEFT PRECORDIUM IN NORMAL AND ABNORMAL CASES

CHEST POSITIONS 5 AND 6

R Wave Normals		*R Wave Abnormals*	
V < CR = RS	34 cases	V < CR = RS	32 cases
V = CR = RS	14 cases	V = CR = RS	13 cases
CR > V = RS	2 cases	CR > V = RS	2 cases

TABLE 7.—SHOWING T WAVE TYPES AMONG NORMAL AND ABNORMAL CASES

NOTE: In 2 of the normal cases the T wave in aV_R could not be measured, while in 4 of the abnormal cases the T waves were unmeasureable

Normal

T Waves	V_1	CR_1	RS_1	V_2	CR_2	RS_2	V_5	CR_5	RS_5	V_6	CR_6	RS_6	aV_R
Inverted	17	2	2	1	—	—	—	—	—	—	—	—	45
Diphasic	8	—	—	1	—	—	—	—	—	1	—	—	—
Isoelectric	9	8	8	2	1	2	2	—	1	2	1	1	3
Upright	16	40	40	46	49	48	48	50	49	47	49	49	—

Abnormal

	V_1	CR_1	RS_1	V_2	CR_2	RS_2	V_5	CR_5	RS_5	V_6	CR_6	RS_6	aV_R
Inverted	12	6	7	5	7	7	19	18	19	21	20	22	24
Diphasic	6	2	2	4	1	1	3	3	3	3	3	4	2
Isoelectric	3	6	5	1	—	—	2	3	1	1	2	—	5
Upright	23	30	30	34	36	36	20	20	21	19	19	18	12

Two cases showed a taller R in $CR_{5,6}$ than in $V_{5,6}$ or $RS_{5,6}$, the latter being equal. Measurements could not be made in 1 case because of the excessive height of the R waves.

Throughout the series no gross variations in the level of the ST junction or segment were encountered.

T wave patterns are represented in Table 7. In the normal group the T

were found at chest positions 5 and 6 in V, CR, and RS. In lead aV_R the T waves were inverted in 45 of 48 cases.

In the abnormal group (Table 7) the T waves in V_1 were inverted or diphasic in 18 of 44 cases, while in CR_1 and RS_1 the T waves were inverted or diphasic in 8 and 9 of 44 cases, respectively. At chest position 2 upright T

waves were present in 34, 36, and 36 of 44 cases for V_2, CR_2, and RS_2, respectively. Similar T wave patterns are exhibited in V, CR, and RS leads from chest position 5 and 6 with almost equal division of the majority of T waves into upright or inverted groups. Only 24 of 43 aV_R leads displayed an inverted T wave.

The T wave changes are compatible with the diagnosis of acute cor pulmonale, although usually the greatest inversion is from the right, decreasing as the exploring electrode is moved toward the left. No support for this diagnosis was found clinically. The QS pattern from the right precordium suggests the diagnosis of anteroseptal

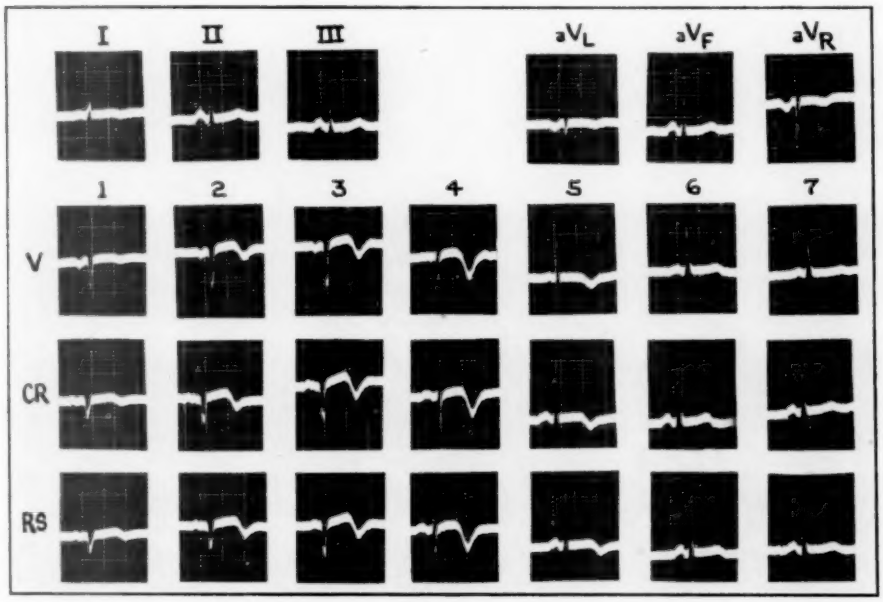

FIG. 1.—Tracing shows differences between V, CR, and RS leads in a case of anteroseptal infarction. Note: Variation in P waves, amplitude of QRS complexes, minute q wave in V_4 and RS_4, and variations in T waves.

Individual tracings were studied to determine whether any of the variations encountered were sufficiently significant to alter the diagnoses. Of the 50 cases classified as normal, no diagnostic differences existed whether the indifferent electrode was V, CR, or RS.

Surprisingly enough, very few of the curves considered abnormal showed any significant differences. Seven cases were diagnosed as suspicious or definite anteroseptal infarction, none recent. Fig. 1 is typical of these cases. infarction and is present in V, CR, and RS. The absence of q waves from the left precordium suggests that the infarct is confined to the septum or extends subendocardially only, into the anterior wall of the left ventricle. In either instance the activation of the septum is from right to left. The lack of slurring of the upstroke of the R from positions over the left chest speaks for the infarct being limited to the septum. Assuming that the exploring electrodes have been correctly placed,

diagnostic points are present in the V leads, not present in the CR or RS leads. The inverted P waves in the V leads indicate that the electrode was far enough to the right over the atrium. At chest position 4 the minute q preceding the S wave is present only in the V and RS but not CR, which anteroseptal infarction in the V_1 and V_2 leads entirely unsuspected from either the CR or RS leads. In this instance the transition zone is at chest position 2 and is of low amplitude because the potential variations of each ventricle tend to cancel each other. It will be noted that aV_R is quite

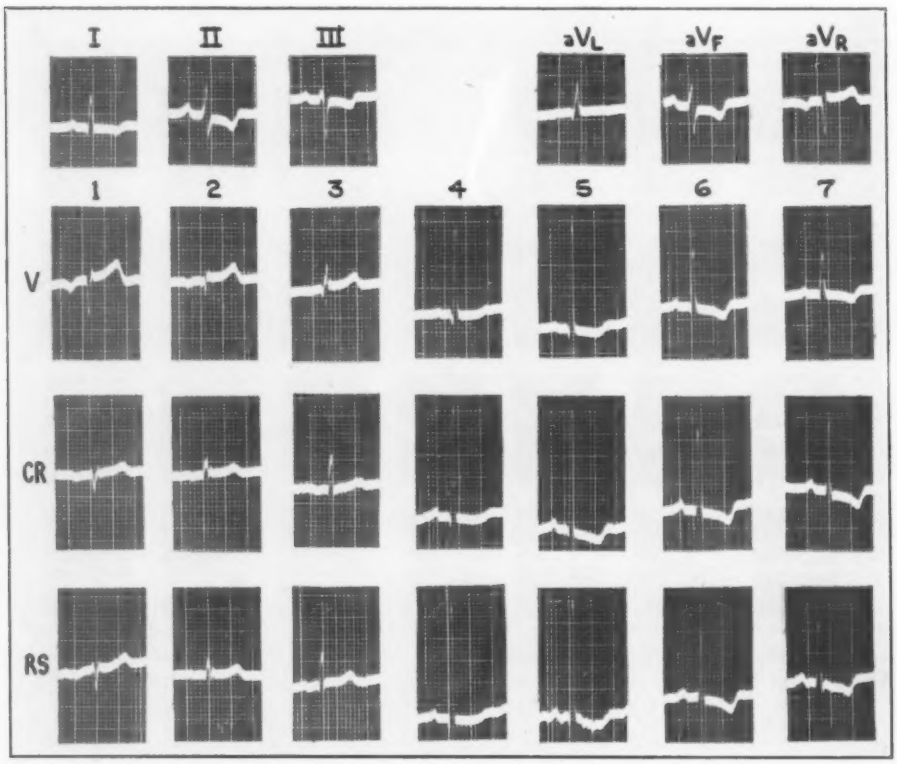

FIG. 2.—Tracing shows borderline left ventricular hypertrophy and suspicion of anteroseptal infarction. Note marked variations between V_2, CR_2, and RS_2

speaks strongly for an infarction being the underlying pathology, rather than an acute cor pulmonale. In addition the non-specific differences generally encountered throughout the series can be seen.

Fig. 2 shows borderline evidence of left ventricular hypertrophy. In addition there is suggestive evidence of an deep. Thus, in CR_2 and RS_2 the curve represents chiefly the potential variations of the right arm and the right scapular area overshadowing the lower voltage from the precordium. This obscures the pattern of the anteroseptal infarction.

The V leads of Fig. 3 show a relatively large R wave without a suc-

ceeding S wave at chest position 1. A prominent Q is noted preceding the R, not present in either CR or RS. The time interval from the beginning of the QRS complex to the onset of the intrinsicoid deflection is abnormally long, and longer than that found in V_6 or V_7. The S wave is prominent in leads $V_{5,6,7}$. These findings indicate right ventricular hypertrophy, although a conduction defect of the outer wall of the right ventricle is not excluded entirely and additional leads farther to the right would have been helpful. Since, however, R in V_2 is taller than R in V_1, in all probability the hypertrophy is of the outflow tract (pulmonary conus) rather than the tricuspid ring[8].

Of 2 cases originally suspected of right ventricular hypertrophy on the basis of the V leads, 1 failed to reveal diagnostic changes in the CR and RS leads. However, without the aid of additional leads from the right precordium the diagnosis was considered tenuous and the tracings were withdrawn from this group.

In other tracings the V, CR or RS leads show left ventricular hypertrophy. No diagnostic differences were encountered among the remaining examples of left ventricular hypertrophy (15), posterior infarction (5), posterolateral infarction (3), or right (6) and left bundle branch block (3).

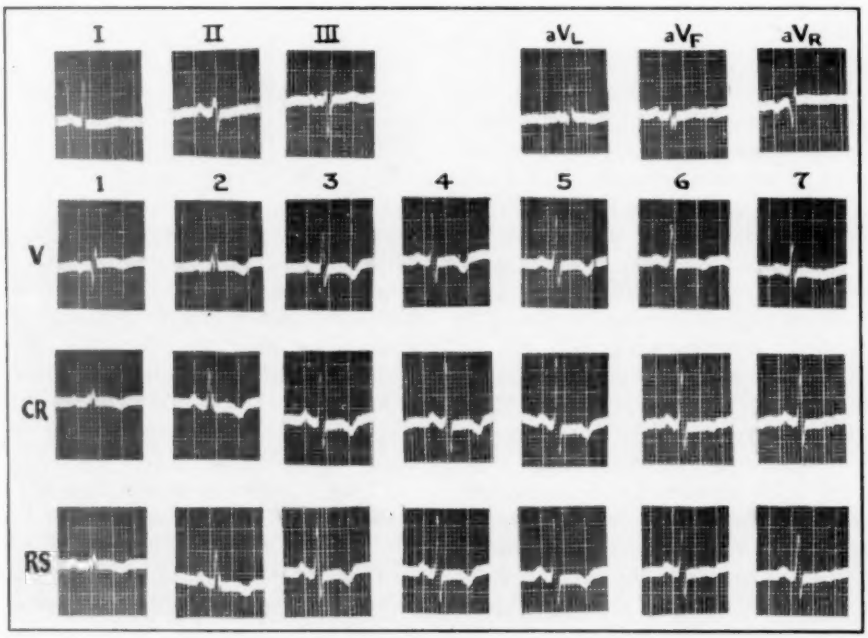

FIG. 3.—Probable right ventricular hypertrophy with prominent Q wave and delayed intrinsicoid deflection in V_1, not seen in CR_1 or RS_1.

Discussion. It is known that the extremity potentials influence the character of the precordial tracings, producing, in effect, a bipolar electrocardiogram. For these reasons the attempt was made to develop an indifferent electrode of zero potential[10,11].

The adoption of the central terminal has not been universal.

Theoretically a CR lead is the algebraic sum of the[4] chest and right arm potentials, but the effect is not equal, for one may dominate the other. Thus, a negative potential in the right arm would add to the positivity of the precordial tracings or a positive potential would increase the negativity. It is known that the right arm potentials are predominantly negative, as this present work shows again, and therefore, the CR electrocardiogram is more positive than a similar curve would be, using the central terminal. Theoretically it should be possible to predict the curve obtained from the CR leads by applying the formula: $V-2/3\ aV_R = CR$. To prove this practically, all points on the curves should be precisely matched, and since simultaneous curves were not available for this study, present comparisons were made on the total QRS measurements.

Right scapular potentials similarly affect the RS electrocardiogram. These potentials have been shown to be similar to those of the right arm[8] when paired with the central terminal. Because the use of the central terminal might seem technically discriminatory when used to prove the lack of indifference of the right scapula, further comparisons between RS leads and comparable known bipolar leads (CR) are presented. Throughout the series the similarity of RS and CR remains evident.

One readily apparent effect of the increase in positivity of the chest leads when the CR and RS electrode is employed is seen in the shift of the transition zone to the right by ½ to 1 chest position. This cannot be attributed to any variation in the position of the heart or to technical procedure, since the tracings were made from the same positions and during 1 period. The mere fact that the transition zone is displaced to the right might be circumvented by recommending leads further from the right, that is, CR_{3R}, CR_{4R}, RS_{3R}, RS_{4R}. Whether or not these leads might be useful remains to be proved. The great similarity between the CR and RS leads must indicate that the two have similar potential variations.

The configuration and direction of the P, QRS, and T waves illustrate the tendency toward increased positivity of these waves in the CR and RS leads. P waves become upright in the CR and RS leads and thus the help obtained in localizing the position of the electrode in relation to the heart and the position of the heart in the chest is lost. The predominantly negative P wave seen in aV_R is considered to be the cause. The greater positivity of the QRS wave is amply demonstrated. The similarity between the T waves over the left chest is more apparent than real, since only the direction of the wave and not the actual measurement is recorded. The position of the heart did not seem to influence any of these observed changes.

From a theoretical standpoint differences should be great enough to alter diagnosis in several conditions. Among these are cases of anteroseptal infarction which might easily be obscured (Figs. 1 and 2), cases in which a high voltage exists in aV_R (Fig. 2), and in certain cases of right ventricular hypertrophy where there is a prominent R in aV_R (Fig. 3). The present series is not notable for a large number of such examples. However, they do occur, and it is hoped that future work will illustrate more of these differences either through a larger number of cases or through a careful selection of examples. Actual differences in diagnostic possibilities have been shown, even in this small series of cases. Furthermore, the small series

emphasizes without question, the similarity between the right arm and the right scapular potentials when their effect, as exerted on the precordial leads, is compared with the central terminal leads. These facts lead normally to the recommendation that the central terminal be employed routinely in all ordinary electrocardiographic work.

Summary. Recognizing the need for standardization of electrocardiographic leads, 98 electrocardiograms taken at Oak Forest Infirmary were surveyed. The following leads were available for study: I, II, III, aV_L, aV_F, aV_R, V_1 through V_7, CR_1 through CR_7, RS_1 through RS_7. The problem posed was whether significant differences existed between the curves depending upon the type of indifferent electrode employed.

In leads from the right precordium both P and T waves were more positive in the CR and RS leads. The QRS complexes showed a similar tendency. In 2 cases, 1 of anteroseptal infarction and 1 of right ventricular hypertrophy, the size and shape of the complexes differed sufficiently among the various leads to result in differing diagnoses.

The variations between the V, CR, and RS leads were attributed to the influence of the right arm potentials as seen in aV_R. In almost all cases aV_R exhibited a predominantly negative deflection which would increase the positivity of the precordial leads when the right arm was used as the indifferent electrode. The striking similarity between corresponding CR and RS leads led to the conclusion that the right scapula is not completely indifferent but exhibited a potential similar to that of the right arm.

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NITROGEN AND POTASSIUM METABOLISM: THE REACTION PATTERN IN POLIOMYELITIS

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The acute poliomyelitis epidemic which affected over 3,000 persons in Los Angeles in 1948 initiated a concerted effort to understand some of the pathological biochemical mechanisms found in this disease. Two phases of this study have already been reported, the alterations in serum protein levels together with the effects of treatment by irradiated human plasma[3], and the changes in serum electrolytes[2].

This study is concerned with the very large losses of nitrogen and potassium occurring in the acute phase of the disease and with the relationship of the magnitude of these losses to the severity of the disease process. These losses are important because they have proven to be of prognostic and therapeutic significance. Data for these observations were obtained from 17 cases on one ward in which intensive biochemical studies were made for periods up to 3 months.

The term "toxic destruction of protein" has been applied to this phenomenon which has been recognized in a large variety of conditions such as acute hemorrhage, surgical operations, traumatic injuries, and various infectious diseases[19]. Recently, Selye has incorporated this concept into the broad framework of the general adaptation syndrome, in which non-specific damaging agents produce a "catabolic impulse" characterized by a breakdown of body proteins[22].

It has already been observed in conditions other than poliomyelitis that the magnitude of the nitrogen loss appears to be related to the ultimate severity of the disease and not to its immediate clinical appearance[19]. The usefulness of this means of assaying the severity of the poliomyelitic case will be apparent from the results of this study.

In addition to these urinary nitrogen manifestations, there are characteristic alterations in the serum proteins such as an abrupt drop in the albumin fraction and also in the free amino acid in the catabolic reaction to injury[18].

These serum protein alterations have been confirmed in poliomyelitis, together with alterations in electrophoretic patterns characterized by increase in alpha and beta globulins[3,15].

Since potassium is the dominant cationic component in protoplasm, its in-

timate relation to the protein changes would be anticipated, but very little information with respect to its metabolism in human poliomyelitis is available.

Data and Methods. OBJECTIVES. The primary objectives of this phase of the biochemical studies were: 1) To determine the existence of abnormalities in protein or potassium metabolism, 2) to correlate if possible the biochemical patterns with the clinical course of the disease, for a better understanding of the physiology of the disease, and 3) to assay the value of these biochemical findings for prognostic and therapeutic purposes.

The techniques used have already been described[2,3]. It should be noted that the albumin globulin fractionation was carried out by the use of 22.5% sodium sulfate (Howe separation)[14,16,17]. Recent work indicates that the albumin fraction so determined includes the alpha globulin, and hence actually the true albumin is lower than that recorded[12].

Blood samples were taken every other day between 10:00 a.m. and 12 noon. Urine was collected for 24 hour periods, daily.

Results and Comments. An analysis of the data obtained on these 17 cases indicates that in general the course of the disease is divisible into 3 phases: an acute catabolic phase, a subacute catabolic phase, and an anabolic phase. Variations from this general pattern occur and are included in the diagrammatic sketch (Figure 1).

TABLE 1.—SALIENT CLINICAL DATA IN 17 CASES OF POLIOMYELITIS.

Severity	*Skeletal Muscle Involvement*	*Anatomical Diagnosis*	*Case*
Mild	Paralysis or involvement of 1 limb only	Bulbar	1
		Bulbar-spinal	1
Moderate	Bilateral severe paralysis of lower limbs and of trunk or respiratory muscles	Bulbar-spinal	1
		Spinal	2
Severe	Severe paralysis of trunk or respiratory muscles or of all 4 extremities	Bulbar-spinal	4
		Spinal	8

SELECTION AND CLASSIFICATION OF CASES. The 17 patients in this study were on a single ward, and all were acutely ill on admission or shortly thereafter. All had respiratory involvement, and nearly all required the use of the respirator. Tracheotomy was performed in 14 patients. These patients were either placed on a specific dietary regimen, or fed parenterally or by gastric drip, so that their intake could be calculated for nitrogen and electrolyte balance studies.

Estimation of the degree of ultimate severity was based on evaluation of the subsequent status of the muscles by physicians and physical therapists 1 to 3 months after admission. Table 1 shows the criteria for this classification, together with the anatomical diagnosis and the number of cases of each type.

BIOCHEMICAL DATA. All chemical work was performed in a research laboratory under the direction of one of the authors (Albert L. Chaney), and included the following: *Blood Serum:* Sodium, potassium, chloride, bicarbonate, pH, albumin globulin, and hematocrit; *Urine:* Sodium, potassium, chloride, and total nitrogen.

The characteristics of each phase will be considered separately.

ACUTE CATABOLIC PHASE. The acute catabolic phase is present in all cases and is characterized by: a) excretion of large quantities of nitrogen and potassium in the urine, indicative of protoplasmic breakdown; b) a rapid drop in serum albumin, accompanied by a rise in the serum globulins. Serum potassium values may range from subnormal to excessively high levels, as will be discussed later.

There appears to be a direct relationship between the duration and magnitude of this excessive protein destruction and the severity of the

disease process as evaluated by neuromuscular examination in the convalescent stage. This is apparent from Table 2 and Fig. 2.

In order to compare results in poliomyelitis with the similar nitrogen losses in other conditions, Table 3 has been compiled[4,5,10,14].

nitrogen ratios. It has been pointed out that, if potassium is expressed in milli-equivalents and nitrogen in grams, the theoretical ratio of these elements is 2.7 to 1 for protoplasmic breakdown[1,11,21]. In actual cases, the ratio is also influenced by the relative intake of potassium and protein and by the state of body reserves. During the acute catabolic phase, this ratio was closely approximated. In the majority of the cases the values ranged from 2.4 to 3.0. As might be anticipated

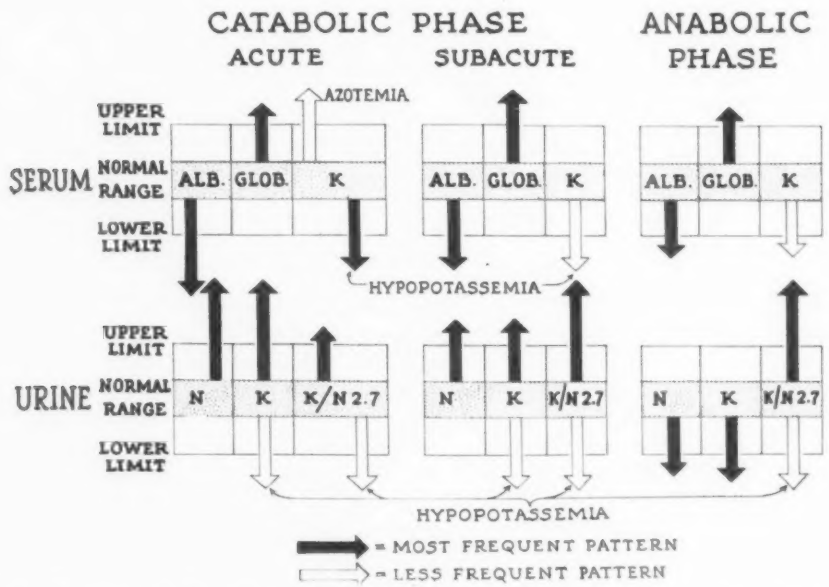

FIG. 1.—The arrows indicate both the direction and the degree of the deviation from the normal. The most frequent pattern is represented by solid arrows, and less common deviations by arrows in outline. Low serum potassiums are accompanied by decreased urinary excretion and a lowered potassium to nitrogen ratio.

TABLE 2.—FEATURES OF ACUTE CATABOLIC PHASE OF POLIOMYELITIS.

Classification	*Time of Peak Nitrogen Excretion*	*Average Peak Nitrogen Excretion, gm./day*
Mild	3rd day after admission	17 gm./day
Moderate	7th day after admission	25 gm./day
Severe	12th day after admission	42 gm./day

RATIO OF URINARY POTASSIUM TO NITROGEN. A useful confirmation of the concept of tissue destruction in this phase may be obtained from the relationship of urinary potassium to

when serum potassium levels were low, indicating depletion of the reserve, the tendency toward conservation of potassium caused the ratio to be less than 2.4. Fig. 3 illustrates these relationships. In some severe cases requiring a respirator and parenteral feeding, the initial excretion of potassium was the dominant factor giving a ratio in excess of 3.0 to 1.

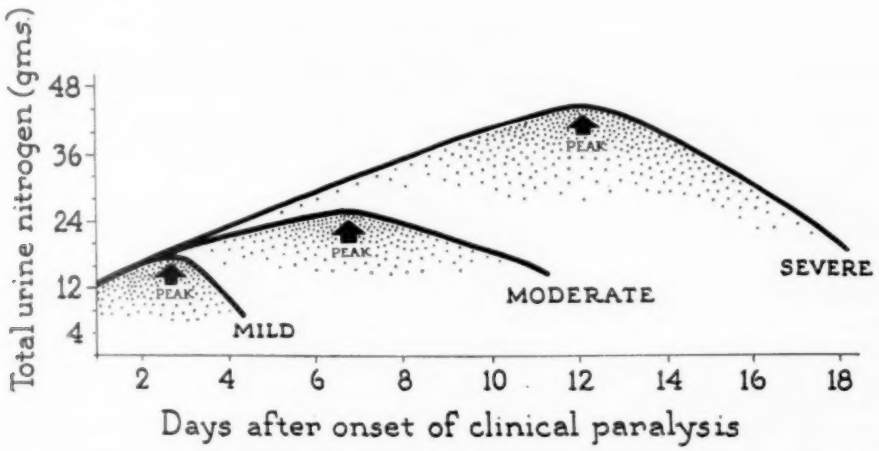

FIG. 2.—Schematic relationship of total nitrogen excretion to severity of neuromuscular involvement in acutely ill patients, in whom minimal residual neuromuscular changes occur reach a peak average nitrogen excretion of 16 gm. on the 3rd hospital day, which promptly decreases to normal. Severe ultimate paralysis is manifested by a progressive rising nitrogen excretion which attains an average peak of 42 gm. on the 12th day with gradual subsidence thereafter. The nitrogen excretion pattern for moderate degrees of involvement is intermediate in character.

TABLE 3.—NITROGEN LOSSES IN CERTAIN OTHER PATHOLOGIC PROCESSES.

Process	*Average Peak Nitrogen Excretions, gm./day*
Trauma (skeletal fractures)	11
Operations (appendectomy)	13
Burns	30
Acute infections	
a) Scarlet Fever	24
b) Pneumonia	34
c) Meningitis	33
d) Meningitis with polyarthritis	141

SUBACUTE CATABOLIC PHASE. The characteristics of the subacute phase are similar to those of the acute phase, but less marked. There is a continued excess of excretion over intake for potassium and nitrogen, but at a lesser rate because of depletion of both reserves. When adequate amounts of potassium are given, the ratio of K:N is primarily determined by potassium intake, and exceeds 3.0 to 1. Serum albumin remains low but may rise gradually, while globulins are persistently elevated, with serum potas-

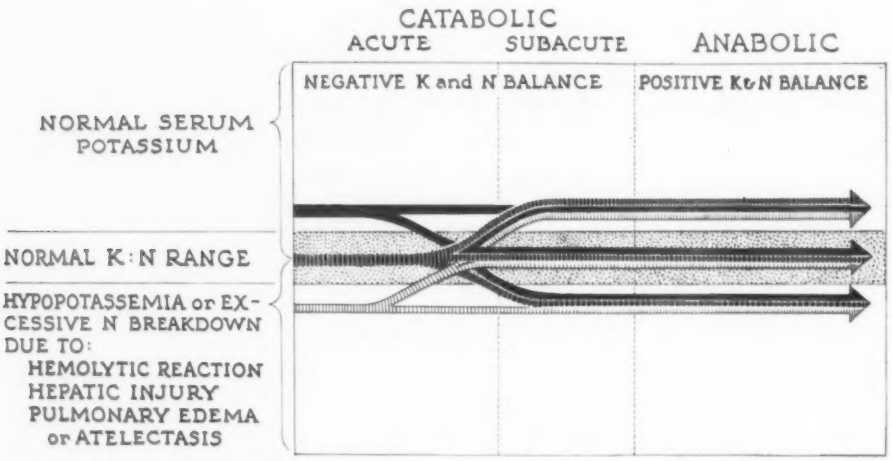

FIG. 3.—Schematic relationship between urinary excretion of nitrogen and potassium. The different patterns occurring during the course of the disease are indicated by the varying pathways shown in the diagram. A primary determining factor is the serum potassium level. With a normal serum potassium, the potassium to nitrogen excretion ratio remains normal or greater than normal. Subnormal ratios are due to hypopotassemia, or complications causing excessive nitrogen breakdown.

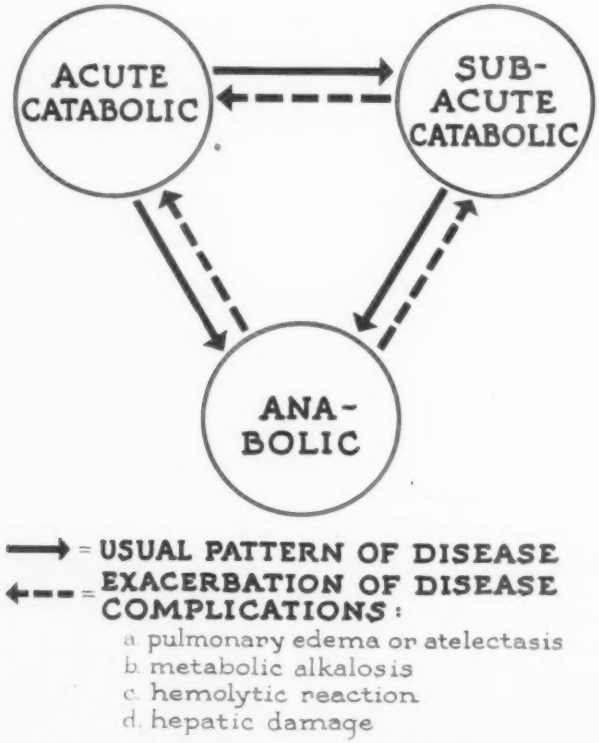

FIG. 4.—Relationship of phases of metabolism.

siums in the normal range unless intake is abnormally low.

This phase was noted in 1 moderate and 5 severe cases and ranged from 2 to more than 30 days in duration.

ANABOLIC PHASE. The anabolic phase is characterized by synthesis of protein with positive balances of potassium and nitrogen. Urinary excretion levels are low, and the ratio of K:N reflects intake and the relative demands in relation to body reserves. Serum albumin values approach normal in "Mild" and "Moderate" cases, but may be persistently low in "Severe" cases for months. Serum globulins remain elevated, and potassium levels are normal except when intake is insufficient to meet the demands of tissue synthesis.

Data on this phase were obtained for approximately 2 months on 6 severe cases.

Deviations from the general pattern occurred in a number of instances and are illustrated in the diagram, Fig. 4. In the mild cases, the subacute phase was minimal or absent. In the severe cases, some terminated fatally in the acute phase and others reverted from the anabolic to the catabolic phase due to other complications or an exacerbation of the original process.

URINARY NITROGEN EXCRETION. The 24-hour urinary nitrogen excretion was found to be the single most reliable index of the catabolic process and of the transition from this to other phases. Those patients in shock with decreased renal output provide the exception to this generalization. Consequently, the duration and magnitude of the catabolic and anabolic periods are based principally upon data obtained from these measurements.

The onset of the acute catabolic process is variable when correlated with the development of detectable paralysis. In 2 cases, a lag in the occurrence of a negative nitrogen balance was noted. In these cases a positive nitrogen balance was still present on the 3rd and 7th days, respectively, after the onset of clinical paralysis. A subsequent negative nitrogen balance then ensued. In 13 cases, the catabolic phase was already evident by the 3rd to 8th days after the onset of paralysis when urine studies were begun.

SERUM PROTEINS. The general pattern of serum protein levels has been reported in a previous analysis of 72 cases[3]. Table 4 and Fig. 5 summarize the findings for the 17 cases of this group in the different phases of the disease.

It will be noted that the drop in albumin is correlated with the severity as judged by the criteria of this study, that in severe cases the levels remain persistently low, and globulins are persistently elevated.

Irradiated plasma at the rate of 5 cc. per pound (body weight) per day for a period of several days was used in a number of cases. It was observed that only a temporary retardation of fall of serum albumin was produced in the severe cases, but in the mild cases a temporary elevation above the initial level sometimes occurred.

SERUM POTASSIUM. Analyses of these data indicate that an adequate intake of potassium ranges from 3 to 5 gm. per day throughout the course of the disease, with sodium requirements ranging from 1 to 3 gm. per day. Since serum potassium levels covering the whole range both above and below normal were found, an elaboration of the factors governing these levels is desirable. These factors are: 1) Potassium (and sodium) daily intake; 2) abnormal losses, as tabulated below; and 3) state of hydration and renal function.

High Potassium Levels are due to 1) dehydration and low renal blood flow; and 2) cell to serum shift due to asphyxia or epinephrin and replacement by sodium.

Low Potassium Levels are due to 1) inadequate intake (anorexia); and 2) excessive loss from a) tissue catabolism; b) metabolic alkalosis from excessive parenteral saline and glucose; c) naso-gastric suction; and d) diarrhea.

Examples of high serum potassium levels are provided in Case 2, and low values are illustrated by Cases 1, 3, 4, and 6.

POTASSIUM–NITROGEN RELATIONSHIPS. As has been previously mentioned, the destruction of tissue is accompanied by the excretion of potassium and nitrogen in a proportion approximately 2.7 mEq. of potassium per gram of nitrogen. During the acute catabolic phase, severe depletion of both protein (as illustrated by serum albumin) and potassium occurs.

Potassium depletion may be rapidly overcome by oral or parenteral administration, but tissue protein and serum albumin are only slowly resynthesized by the liver. The rate of synthesis appears to be related to the severity

TABLE 4.—AVERAGE SERUM ALBUMIN AND GLOBULIN VALUES IN THE SEVERAL PHASES OF 17 CASES OF POLIOMYELITIS.

	Acute Catabolic		*Subacute*		*Anabolic*	
	Alb. (gm.)	Glob. (gm.)	Alb. (gm.)	Glob. (gm.)	Alb. (gm.)	Glob. (gm.)
Mild	4.3	2.8	—	—	4.7	2.8
Moderate	4.0	2.9	—	—	4.4	2.9
Severe	3.4	3.0	3.6	3.2	4.1	3.4

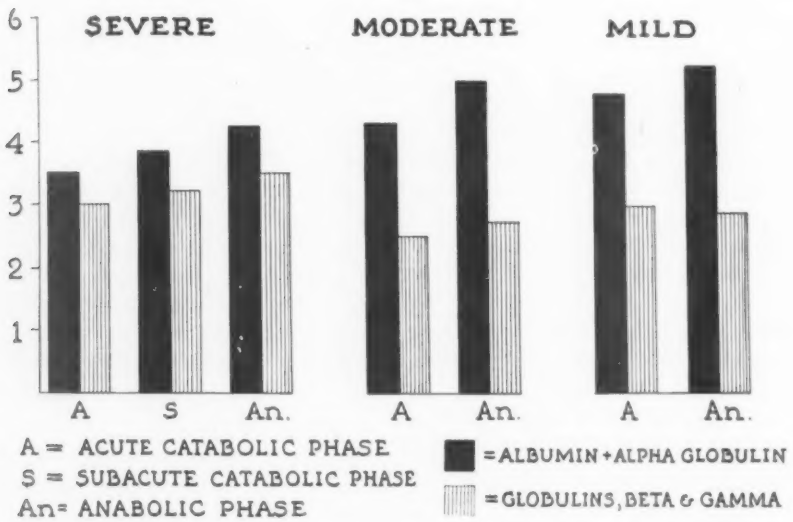

FIG. 5.—Serum protein changes during catabolic and anabolic phases.

of the catabolic process, being very slow in the severe cases and more rapid in the mild.

The relationship of potassium and nitrogen is particularly useful in judging the potassium requirements. A low K:N ratio during the acute catabolic phase is indicative of severe potassium depletion. Potassium deficits are due to excessive urinary loss (catabolic phase) and to increased retention accompanying tissue synthesis (anabolic phase).

inal reflexes; bladder paralysis, and paresis of both legs, but no intercostal or diaphragmatic weakness.

Spinal Fluid Findings were: a ground glass appearance, sugar normal, Pandy 1 plus, total protein 93 mg. per 100 cc., 116 cells; 52 polymorphonuclears, and 64 lymphocytes.

Course. With development of intercostal weakness and breathing difficulty, the patient was kept in the respirator from the 6th to the 12th day after admission. Vital capacity was 52% 2 weeks later. Hypertension ranged from 160/100 to 170/110 and was continuously present.

Final Evaluation showed marked paralysis of both legs, considerable weakness in the

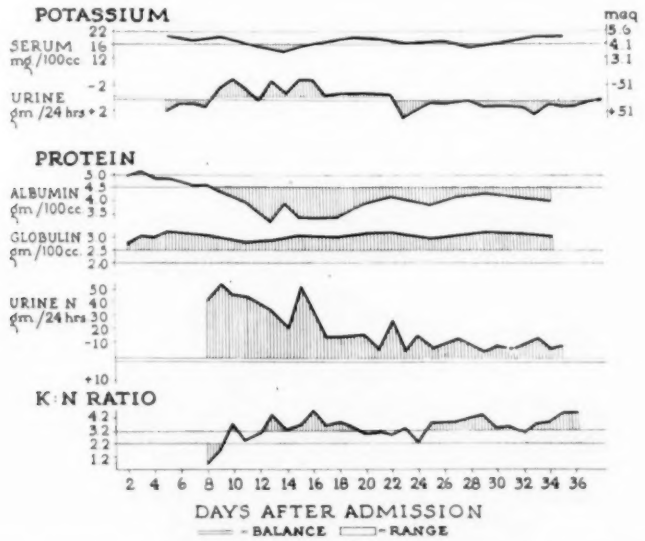

FIG. 6.—Changes observed in uncomplicated severe poliomyelitis, Case 1, W.R., male, aged 21 yr. (The potassium and nitrogen balance shown in this and subsequent diagrams are the total urinary excretions less the corresponding intake.)

Case Histories. These relationships are illustrated in the following 6 case histories. The biochemical findings are shown graphically in Figs. 6 to 11.

SEVERE POLIOMYELITIS. CASE 1. A Caucasian male, aged 21, had lumbar backache 5 days before admission, followed by headache, fever, malaise, stiff neck, nausea, vomiting, and urinary retention, and marked weakness of both legs.

Clinical Examination showed him to be well developed. Neurological findings included marked stiffness of neck and hamstring muscles, absent deep tendon reflexes and abdominal diaphragm and the right arm, bladder paralysis, and scattered weakness of intercostal and neck muscles.

Comment. This is a severe catabolic process followed for 36 days with change from acute to subacute estimated at the 17th day. There was high nitrogen excretion from the 8th to 18th day with 67 gm. on the 10th day. Lesser negative nitrogen balance continued from the 18th to the 36th day.

The albumin level of 3.3 gm. on the 19th day increased to 4.3 gm. Globulin ranged from 3.1 to 3.6 gm. Hypopotassemia was present from the 12th to the 15th day, preceded by 4 days of large urinary potassium excretion accompanying peak nitrogen excretion. Subsequent serum and urine potassium levels were normal.

intercostals; paresis of both legs, left ankle jerk absent, positive Babinski reflexes bilaterally.

Spinal Fluid Findings were: a ground glass appearance, Pandy trace; normal sugar, 34 cells; 28 lymphocytes, and 6 polymorphonuclears, culture Staphylococcus aureus, coagulase negative.

Course. Tracheotomy was performed and the patient placed in a respirator and plasma therapy instituted on admission. Cyanosis

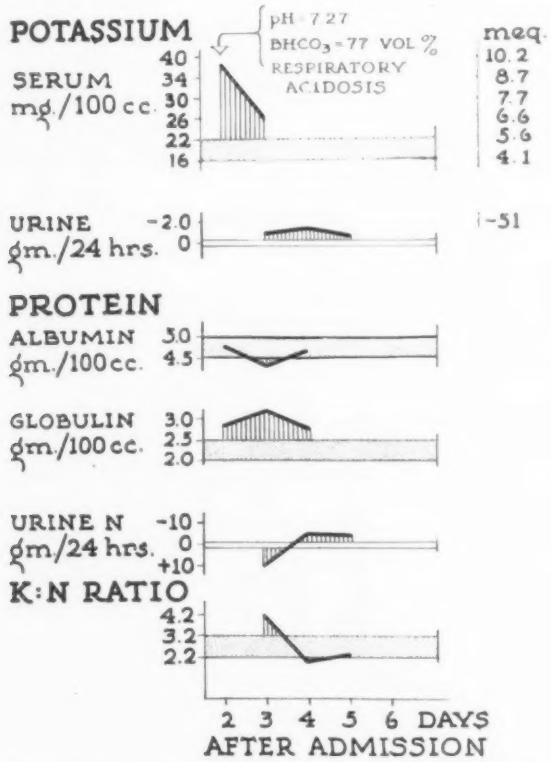

FIG. 7.—Changes observed in severe poliomyelitis with complications, Case 2, M.P., female, aged 25 yr. (See Fig. 6 for explanation.)

CASE 2. A white female, 25 years old, and 5 months pregnant, had cough and sore throat 6 days prior to admission, followed by headache, slight fever, weakness in both legs, and difficulty in breathing and swallowing.

Clinical Examination disclosed cyanosis and acute respiratory distress, excessive mucus in oropharynx and coarse rales in both lungs; a tachycardia of 130 per minute. Neurological findings included dysarthria, dysphagia, jerky diaphragmatic movements and paralysis of

persisted, and the patient expired in 4 days in spite of all known supportive treatment.

Autopsy. The findings were consistent with acute poliomyelitis. In addition to marked destruction of the anterior horn cells in the medulla and spinal cord, there was pathological evidence of encephalitis with hemorrhage into the corpus callosum.

Comment. The patient was in shock on admission and remained so until

death. Urinary nitrogen excretion was accordingly low and paralleled urine volume due to low renal blood flow. Albumin decreased from 4.9 gm. to 4.5 gm., and globulin increased from 2.9 gm. to 3.3 gm. Serum potassium level was excessively high, 37 mg. and 26 mg., with no potassium intake.

Course. There was inability to swallow, intercostal and right leg paralysis 2 days after admission. Tracheotomy was performed and the patient placed in a respirator. Progressive involvement of the left leg and both arms was noted on the 24th day, with nausea, cramps, nervousness, and persistent headache. Sodium intake was inadvertently increased to an average of 9 gm./day by plasma and whole blood transfusions. The patient

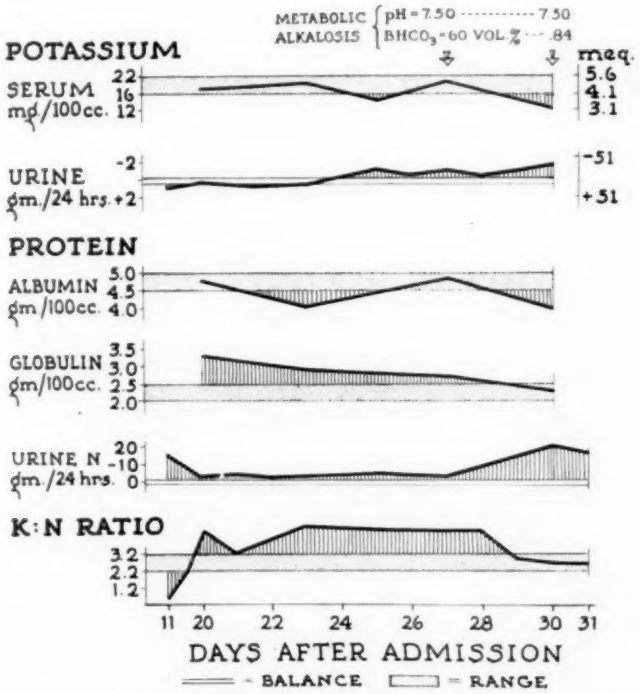

FIG. 8.—Changes observed in severe polimyelitis, Case 3, C.H., female, aged 27 yr. (See Fig. 6 for explanation.)

CASE 3. A white female aged 27, had headache, backache, and pain in thighs 2 days before admission, a temperature of 100° F., vomiting and diarrhea, but no muscular weakness.

Clinical Examination showed her to be well developed and nourished, appearing moderately ill. Blood pressure was 120/86, tachycardia 110 per minute. Neurological findings included moderate back stiffness, tenderness and hypersensitivity of both thighs.

Spinal Fluid Findings were: a ground glass appearance, Pandy trace; sugar normal, 239 cells; 139 polymorphonuclears, and 100 lymphocytes.

succumbed after 6 days of semi-comatose state, with incontinence, fever, and constant frothy mucous discharge. Severe metabolic alkalosis ensued terminally, with blood pH 7.50, and a serum bicarbonate of 84 vol. per 100 cc.

Comment. The patient progressed from preparalytic to severe bulbar-spinal poliomyelitis. An acute catabolic phase was apparently precipitated by the high sodium intake. Hypopotassemia and increased urinary loss of potassium and nitrogen followed, being

more pronounced in the last 2 days of illness, with metabolic alkalosis.

CASE 4. A white male, 27 years old, had abdominal pain 3 days before admission, without vomiting or diarrhea, with headache, fever, vomiting, and left arm weakness on admission.

Clinical Examination showed him to be well developed and nourished, appearing acutely ill. Blood pressure was 140/90, with diminished breath sounds. Neurological findings were moderate stiffness of the back and neck, weakness of the intercostals and arms, paralysis of the legs.

the 22nd day with edema of the glottis. Roentgenogram showed elevation of diaphragm and pulmonary infiltration indicating atelectasis. Weakness of the arms and intercostal muscles and severe paralysis of both legs were still present after 2 months.

Comment. This case illustrates the aggravation of a hemolytic reaction in severe poliomyelitis. Nitrogen excretion averaged about 100 gm./day for 5 days, compared with 40 to 60 gm. for severe poliomyelitis only. The acute catabolic phase lasted the first

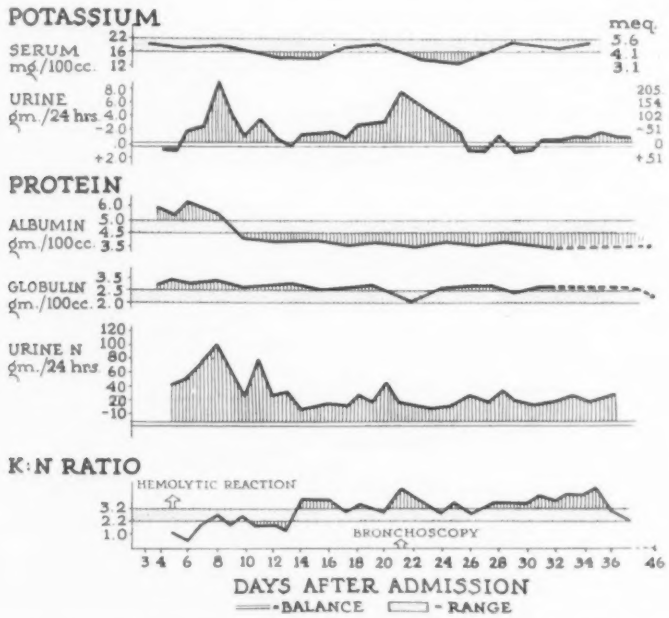

FIG. 9.—Changes observed in severe poliomyelitis, Case 4, R.D., male, aged 27 yr. (See Fig. 6 for explanation.)

Spinal Fluid Findings were: a slightly cloudy appearance; Pandy trace; normal sugar, 197 cells; 101 polymorphonuclears, 96 lymphocytes.

Course. He was placed in a respirator and given 750 cc. of plasma per day for 5 days. Whole blood transfusion was given on the 5th day, with hemolytic reaction and clinical jaundice, with hemoglobin drop from 14 gm. to 8.3 gm. The liver was tender and enlarged; cephalin flocculation was 3 plus, and the icterus index 39 units. Cyanosis appeared on

14 days, with more nitrogen than potassium excreted. A subacute phase followed with atelectasis and with excessive potassium loss predominant and low serum potassium levels. Albumin dropped from 6.2 gm. to 3.5 gm. and remained low.

MODERATE POLIOMYELITIS. CASE 5. A Negro male, aged 13, had headache, anorexia and malaise 4 days before admission, followed by weakness of the left arm.

Clinical Examination showed him to be well developed and nourished, appearing mildly ill. Blood pressure was 118/80. Neurological findings included moderate stiffness of neck, back, and hamstring muscles, left biceps, and left anterior thigh muscles, with slight intercostal weakness.

Spinal Fluid Findings were: Slightly cloudy; Pandy trace; total protein 51 mg. per 100 cc., 32 cells; 28 lymphocytes, 4 polymorphonuclears.

potassium and albumin normal; K:N ratio 2.7. The anabolic phase followed immediately.

MILD POLIOMYELITIS. CASE 6. A white male, aged 9, had malaise, pain in the back and neck, and a temperature of 101° F. 4 days before admission, followed by lethargy and difficulty in swallowing and speaking.

Clinical Examination showed him to be unable to talk or swallow, appearing acutely

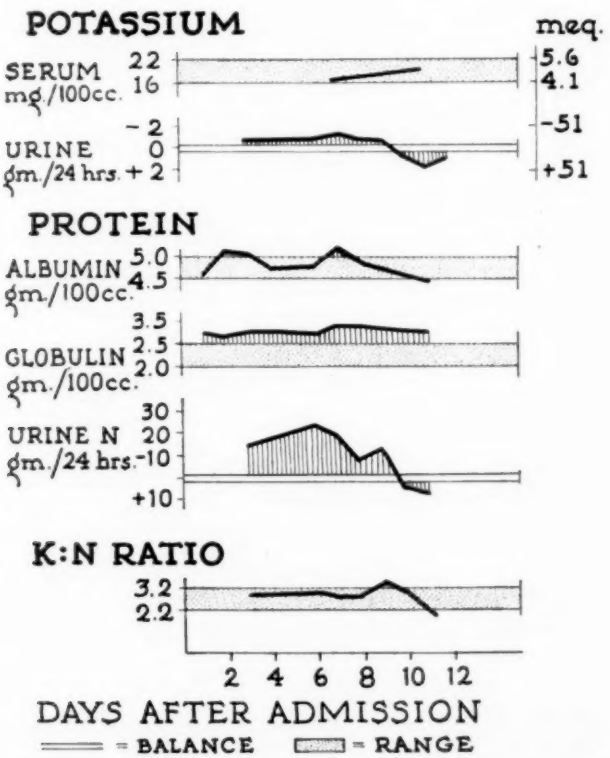

FIG. 10.—Changes observed in moderate poliomyelitis, Case 5, J.S., male, aged 13 yr. (See Fig. 6 for explanation.)

Course. A respirator was unnecessary; hypertension ranged from 132/94 to 145/100 from the 4th to the 14th day; the clinical course was otherwise mild. Patchy weakness of the left biceps and thigh muscles remained 2 months after admission.

Comment. Acute catabolic phase lasted the first 10 days, with peak nitrogen 22 gm. on the 6th day, serum

ill, with much mucus in the throat. Neurological findings included lateral nystagmus; left facial, uvular, and palatine paralysis, deviation of the tongue to the right; moderate stiffness of the back and hamstring muscles; and moderate weakness of the intercostal muscles.

Spinal Fluid Findings were clear, Pandy negative, normal sugar, 61 cells; 54 lymphocytes, 7 polymorphonuclears.

Course. Tracheotomy was performed and the respirator was used for 5 days. Plasma therapy was given, and recovery was uneventful. Muscles of swallowing and neck flexors were moderately weak 1 month after admission.

Comment. The acute catabolic phase lasted 4 days; albumin was normal except on the 10th day; serum potassium was low (no intake until the 8th day), urinary potassium was 0.3 gm./day, the K:N ratio was very low for 16 days.

Recent studies confirming this viewpoint are a low eosinophil count on admission in 70 cases of acute poliomyelitis, suggesting the "alarm reaction." The administration of ACTH to 35 cases produced further depression of eosinophil count and increased 17-ketosteroid excretion; however, no beneficial effect was noted following such therapy[6].

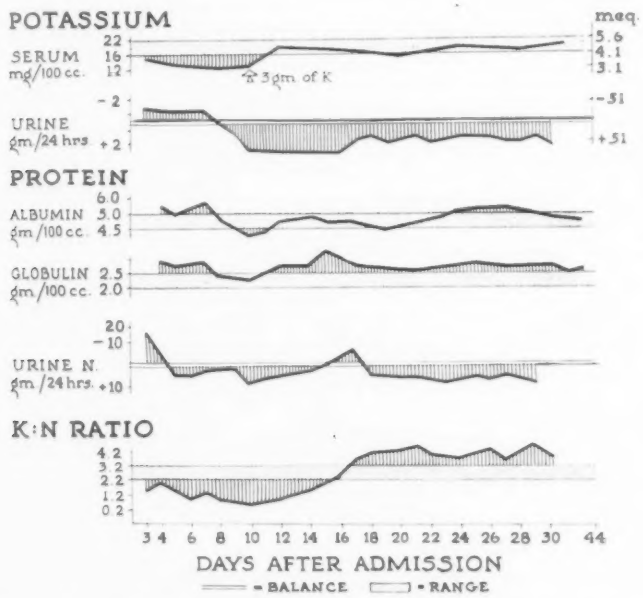

FIG. 11.—Changes observed in mild poliomyelitis, Case 6, S.S., male, aged 9 yr. (See Fig. 6 for explanation.)

Discussion. The profound negative nitrogen and potassium balance during the catabolic phase of the disease and the frequent hypertension fall within the framework of Selye's general adaptation concept[22]. There is apparently extreme stimulation of the anterior pituitary by the "catabolic" impulse of the poliomyelitis virus, with profound influence upon suprarenal and renal physiology.

The fate of the nitrogen compounds resulting from the "toxic destruction of protein" has generally been found to be in increased urinary urea and ammonia, and this is the case with dietary protein in excess of that utilized by the body[20]. Recent work indicates that the administration of ACTH may also increase the excretion of creatine[23].

In both human and experimental forms of poliomyelitis large amounts of creatine in the urine have been recognized[9]. In mice, the creatinurea

appears shortly before paralysis and may reach levels of 3 gm. per liter, and is accompanied by a drop in the muscle creatine[8].

Therapeutic and Prognostic Implications. 1. PROTEIN METABOLISM. The abrupt drop in serum albumin and the accompanying marked urinary nitrogen excretion may lead to shock and peripheral vascular collapse in severe cases of poliomyelitis. The beneficial effects of therapy by serum albumin or irradiated human plasma have already been reported[3].

Daily measurements of the total urinary nitrogen excretion, or less preferably the nitrogen concentration, provide a valuable guide of: a) The degree and the duration of protein destruction which parallels the ultimate severity of the disease process and the amount of residual neuromuscular paralysis that may be anticipated; b) the transition of the catabolic phase into the period of protein synthesis, and conversely; c) the reactivation of a catabolic process due to extension of the pathological process and to the respiratory, electrolyte, hemolytic, and hepatic complications.

It has been difficult for the clinicians to predict the extent of the neuromuscular involvement with any degree of certainty during the early phase of the disease. The use of the total 24-hour nitrogen excretion provides a new means of estimating the ultimate course and the degree of neuromuscular involvement, if the patient survives the initial shock and respiratory complications. If 24-hour nitrogen excretions are not feasible, similar information may be obtained from urine nitrogen concentrations alone, provided normal urine volumes are present.

The clinically severe cases in which extensive paralysis is expected have a prolonged and marked negative nitrogen balance and anatomically are usually of the bulbar-spinal and spinal types. The clinically severe cases in which minimal paralysis is anticipated have a brief and minor negative nitrogen balance, and fall into all 3 categories: Bulbar, bulbar-spinal, and spinal.

2. POTASSIUM METABOLISM. Plasma determinations of this constituent are essential before parenteral therapy is started. Marked elevation of serum potassium may occur in acutely ill patients who have shock, respiratory acidosis, or renal disease, and may produce disturbances of cardiac rhythm leading to ventricular fibrillation[7].

Abnormally low serum potassium may also occur in any phase of the disease if intake is inadequate or excessive catabolic losses occur. This may be prevented by the oral or parenteral administration of 3 gm. or more of potassium daily. Potassium deficiency may accentuate muscle paralysis and cause electrocardiographic disturbances and paralytic ileus[7]. Recent evidence indicates that potassium therapy may also inhibit the catabolic effect of ACTH and facilitate protein synthesis[24].

Exacerbations of the acute catabolic phase, with renewal of increased potassium excretion, require careful attention. Such may occur following atelectasis and subsequent anoxia, hepatic and hemolytic complications, or excessive sodium intake. Sodium requirements range from 3 gm. daily in the catabolic phase to 1 gm. in the anabolic, and excessive intake should be avoided.

Summary. 1. The marked negative nitrogen balance that occurs in the acute phase of poliomyelitis may be utilized as a valuable prognostic aid in predicting the ultimate neuromuscular involvement.

The necessary biochemical determinations are the 24-hour nitrogen

excretions, or less preferably, urinary nitrogen concentrations when urine volume is adequate.

This negative balance is accompanied by a precipitous drop in serum albumin, elevation of the globulin fractions, and a negative potassium balance.

2. Therapeutically, the rapid drop in serum albumin is an indication for the use of serum albumin or irradiated plasma for the prevention of peripheral vascular collapse.

Hypopotassemia, which is frequently present and may be detected by serum determinations, may be prevented by the administration of 3 gm. or more of potassium daily.

Hyperpotassemia may be found with shock and respiratory acidosis, in which case therapy is primarily directed toward restoration of the pulmonary ventilation, diffusion, and improvement of peripheral vascular tone while withholding oral or parenteral potassium.

Excessive sodium intake should be avoided, particularly during the acute catabolic phase when it may predispose to hypopotassemia and metabolic alkalosis. Average requirements at this time approximate 3 gm., and decrease to 1 gm. during the subsequent anabolic phase.

3. During the course of the disease occurrence of complications such as extension of the disease process, pulmonary edema or atelectasis, respiratory acidosis, metabolic alkalosis, and hemolytic reactions with hepatic involvement may be detected early by recurrence of increased nitrogen and potassium excretion.

Grateful acknowledgment is made to the technical and professional staffs of the Communicable Disease Unit, Los Angeles County General Hospital, and to the College of Medical Evangelists, without whose help this study would not have been possible. Aided by a grant from the National Foundation for Poliomyelitis.

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LYMPHOPENIA IN DIAGNOSIS OF THE ACUTE ABDOMEN

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In 1948, Herfort[5] reported that absolute lymphopenia occurred in every one of 29 proved cases of acute pancreatic necrosis, and that this finding was an important aid in establishing the diagnosis when the total white blood count was normal and the amylase test was not significantly altered. He did not find lymphopenia in other acute abdominal conditions which might be confused with acute pancreatitis, such as cholelithiasis, nephrolithiasis, or perforated peptic ulcer. An expanded study[6] by the same author included 38 cases of acute pancreatic necrosis. In this group lymphopenia was absolute in 63.1% and relative in 36.9%. Repeated lymphocyte counts were found to be of prognostic value; that is, the severer the disease, the slower the return of the lymphocyte count to normal. Roberts *et al.*[10] have substantiated the occurrence of lymphopenia in acute pancreatic necrosis, reporting an absolute lymphopenia of less than 1500 lymphocytes in 86% of their 15 cases.

The studies of Selye[11] indicate that the body reacts in a stereotyped manner to various forms of stress, whether it be infection, intoxication, trauma, nervous strain, heat, cold, muscular fatigue, or Roentgen-ray radiation. Among these reactions are inhibition of lymphoid tissue and lymphopenia. It would seem reasonable that the lymphopenia occurring in acute catastrophes would not be limited to pancreatitis, but might occur in all conditions in which stress is a major factor. With this in mind, we have determined the frequency of lymphopenia in a variety of acute abdominal and other conditions to evaluate its significance in diagnosis.

Method and Materials. Private hospitals were selected for this study because in these hospitals the hemograms were performed by trained laboratory technicians. A study was made of the white blood counts in a variety of acute conditions. All hemograms, unless otherwise stated, were the initial counts done on admission of the patient to the hospital. These counts were done before any attempt at definitive therapy had been instituted in order to exclude additional causes of lymphopenia.

Only cases with a verified diagnosis were accepted in this study. The diagnosis of pancreatitis was made at operation, autopsy, or clinically by the presence of an elevated serum amylase. All cases of cholecystitis, both acute and chronic, were histologically proved. The cases of myocardial infarction had typical clinical symptoms and confirmatory electrocardiographic changes. Second or third degree burns were accepted if at least 10% of the body surface was involved; first degree burns were accepted only if more extensive lesions were present. The remaining conditions were diagnosed radiologically, surgically, or at autopsy. In order to get a sufficient sampling of pancreatitis and dissecting aneurysm, the records of 4 private hospitals* were reviewed.

*Records of the White Memorial Hospital, Glendale Sanitarium and Hospital, Loma Linda Sanitarium, and the San Antonio Community Hospital (Upland, California) were reviewed in this study.

Lymphopenia is expressed as either absolute or relative. Absolute lymphopenia refers to a decrease in the total number of lymphocytes per cubic millimeter of blood, whereas relative lymphopenia refers to a decrease in the percentage of lymphocytes in the total white count.

The normal percentage of lymphocytes of the total white blood cells is said to be 20 to 25% by Downey[3], 15 to 60% by Osgood[9], and 25 to 33% by Kolmer[8]. The absolute number is said to be 1500 to 3000 per c.mm. by Kolmer[8], 1000 to 4500 per c.mm. by Osgood[9], and 1200 to 2000 per c.mm. by Beck[1].

cates that a relative lymphopenia below 20% occurred in 86% of our cases of acute pancreatitis. The frequency of relative lymphopenia was comparable in perforated duodenal ulcer, dissecting aneurysm, acute appendicitis, and acute cholecystitis. Pancreatitis produced a relative lymphopenia below 10% more often than the other acute emergencies, but not significantly so. Lymphopenia below 10% was pres-

TABLE 1.—LYMPHOCYTE STUDIES IN ACUTE CONDITIONS

		Relative lymphopenia						*Absolute lymphopenia*			
		Below 20%		*Below 15%*		*Below 10%*		*Below 1500 /c.mm.*		*Below 1000 /c.mm.*	
Disease	*Total No. of cases*	*No. of cases*	*% of total*	*No. of cases*	*% of total*	*No. of cases*	*% of total*	*No. of cases*	*% of total*	*No. of cases*	*% of total*
Acute pancreatitis	38	33	86	29	76	21	55	24	63	10	26
Acute appendicitis	26	21	80	20	76	11	42	12	46	7	26
Acute cholecystitis	21	16	76	12	57	7	33	10	47	4	19
Chronic cholecystitis	26	2	7	1	3	1	3	2	7	0	0
Perforated duodenal ulcer	22	20	90	17	77	9	40	9	40	4	18
Perforated gastric ulcer	14	9	64	6	42	2	14	3	21	1	7
Intestinal obstruction (adhesions, tumor, or infarction)	17	12	70	10	58	7	41	11	64	3	17
Vesical or ureteral calculus	18	13	72	4	22	3	16	6	33	2	11
Renal calculus	16	9	56	3	18	3	18	3	18	3	18
Myocardial infarction	27	21	77	14	51	5	18	7	25	0	0
Skin burns	16	6	37	6	37	1	6	3	18	0	0
Dissecting aneurysm	8	7	87	7	87	3	37	6	75	2	25
Bone fractures	24	17	70	7	29	3	12	5	20	3	12
Arteriosclerotic abdominal aneurysm with rupture	6	5	83	5	83	4	66	3	50	3	50

Because of the differences for the normal values in standard texts and also as an aid in determining specificity of the lymphocyte count, we have arbitrarily expressed the relative lymphocyte count as below 20%, below 15%, or below 10% of the total white cells in Table 1. In the same table is given the absolute lymphocyte count expressed in values below 1500 and below 1000 per c.mm.

Results. Analysis of Table 1 indi-

ent in 55% of the cases of pancreatitis, 42% of the cases of acute appendicitis, and 40% of the cases of perforated duodenal ulcer. Sixty-three per cent of the cases of acute pancreatitis had an absolute lymphopenia below 1500 cells. Lymphopenia of this degree was more frequent, however, in cases of dissecting aneurysm (75%) and intes-

tinal obstruction (64%). Depressions of the lymphocytes below 1000 were equally frequent in acute appendicitis and acute pancreatitis (26%), and the frequency in dissecting aneurysm was almost identical (25%).

Discussion. These figures indicate that both relative and absolute lymphopenia occurs in pancreatitis, but is not unique to this disease. Changes in the definition of what constitutes relative and absolute lymphopenia did not serve to increase the definitive value of the lymphocyte count in diagnosis.

Analysis of our data in 38 cases of acute pancreatitis reveals an absolute lymphopenia below 1500 in only 63% of the cases. Our analysis of Herfort's data indicates that 89% of his cases fell in this group, as did 86% of Roberts' cases. Only 26% of our cases of acute pancreatitis had lymphocyte counts below 1000, whereas 63% of Herfort's cases had such depressions. The relative lymphocyte counts were below 15% in every one of his cases, but in only 76% of ours. The reliability of the laboratory work in our cases is suggested by comparable findings in 4 different hospitals. The discrepancy between Herfort's data and ours is probably explainable on the inclusion in our series of several cases of mild pancreatitis as indicated by rapid recovery, but with sufficient elevation of amylase to make the diagnosis cer-

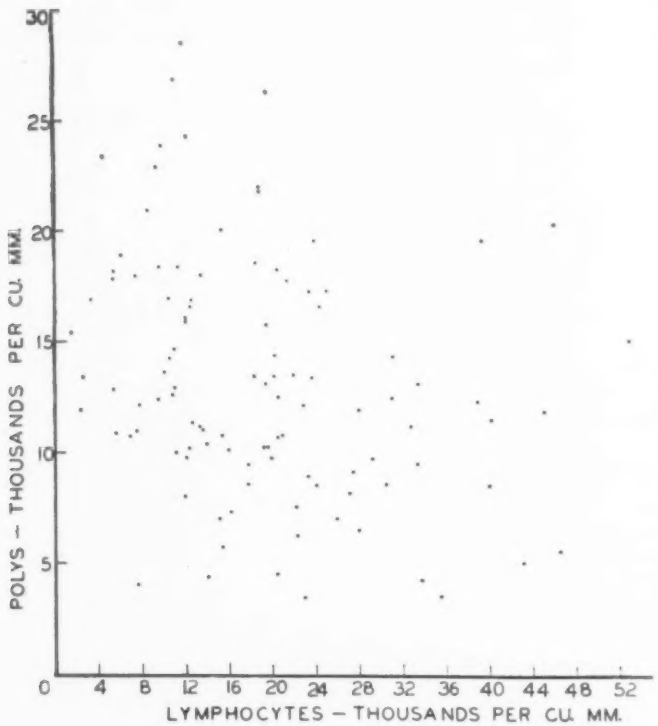

FIG. 1.—Scattergram plotting total lymphocyte against total polymorphonuclear counts in acute conditions.

tain. It is significant that depressions of blood lymphocytes, both relative and absolute, occurred in conditions other than acute pancreatitis with sufficient frequency to make the determination of the lymphocyte count of little diagnostic value.

It is generally believed that the depression in the level of blood lymphocytes occurring in acute conditions is reciprocal to an increase in polymorphonuclear leukocytes. We were unable to demonstrate any relationship between the height of the polymorphonuclear count and the lymphocyte level as indicated by the scattergram (Fig. 1) which includes various acute conditions of this study. Furthermore, our studies show that lymphopenia may occur with low, normal, or high total white blood counts. The evidence suggests that the depression of lymphocytes in acute conditions is selective, occurring independent of the polymorphonuclear leukocyte count.

The common denominator of all the acute catastrophes in this study is stress, whether it be due to trauma, intoxication, or infection. Selye[11] has shown that the characteristic reactions to stress require the presence of an intact pituitary–adrenal axis, the adrenal cortex being stimulated by the adrenotrophic hormone. Dougherty and White[2] have shown that the pituitary adrenotrophic hormone is a prime factor in the regulation of the level of the blood lymphocyte count, its action being mediated through the adrenals. Adrenalectomy was found to abolish the lymphopenic action of adrenotrophic hormone in mice. Adrenal cortical steroids except desoxycorticosterone were found to be active in the production of lymphopenia. Lymphopenia has also been observed in man following injection of adrenocorticotrophic hormone[7] or adrenal cortical extract[2].

Further evidence of increased adrenal cortical activity in stress is suggested by the finding of increased excretion of urinary cortins in man occurring during infections[12,13] and trauma[12,14]. Edmondson[4] has recently reported increased 17-ketosteroid excretion in a case of acute pancreatitis.

In our study, the degree of absolute lymphopenia was proportional to the invoking stress with maximal responses encountered in pancreatitis, dissecting aneurysm, intestinal obstruction, and ruptured arteriosclerotic abdominal aneurysm. Milder responses occurred in acute appendicitis, acute cholecystitis, and perforated duodenal ulcer. A minimal response occurred in perforated gastric ulcer, urinary calculi, myocardial infarction, burns, and fractures. Chronic cholecystitis gave the least response. The tendency for ruptured duodenal ulcer to evoke a greater lymphopenic response than perforated gastric ulcer is probably due to the greater degree of peritoneal irritation associated with higher gastric acid values usually encountered in the former condition.

It follows that lymphopenia is an unfavorable sign in the leukocytic picture. Conversely, as Herfort[6] has suggested, a return of the lymphocyte count towards normal in pancreatitis suggests a good prognosis. It appears that a return of the blood lymphocytes towards normal in any acute condition suggests a good prognosis.

Summary. 1. Lymphopenia, both absolute and relative, occurs in a variety of acute conditions but is not diagnostic.

2. Lymphopenia produced in acute conditions is roughly proportional to the severity of the invoking stress.

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THE CURRENT USES OF CORTISONE AND ACTH

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DRAMATIC results have followed the empirical use of cortisone and ACTH (corticotropin) in so many diseases that a difficult therapeutic problem presenting itself nowadays is not apt to pass by without at least a question of giving these drugs a trial. Such trials involve several problems: There is the fact that the drugs are very costly; also the fact that, aside from exerting important therapeutic actions, they also possess dangerous properties. Before a trial is justified their value must be established by reliable evidence.

A theory which involves these drugs, the *general adaptation syndrome* of Selye[4,5], has developed somewhat faster than clinical evidence has been gathered. It postulates a rigid pattern of adjustments (including the discharge of ACTH from the pituitary) initiated by any stress-producing situation, and presumably helpful in overcoming the difficulty. Derangements of the reaction pattern result in many diseases, which differ in their manifestations by reason of "conditioning" of principal pathways or target organs, but all of which originate from stress: *The Diseases of Adaptation.* Among these, many might be expected to respond to cortisone or ACTH.

There has been a tendency to confuse theory and therapeutic evidence. In our present state of knowledge, the use of cortisone and ACTH in medical practice can be justified only by results, and not by theoretical considerations. Accordingly, this report reviews the diseases in which there is good evidence that cortisone and ACTH are of value, describes the therapeutic results that may be expected, and supplies references to informative articles in the literature. There are no directions for use of the hormones, nor is there an attempt to assign priority. Several recent publications discuss these aspects of the problem[1-3,6,7]. Dis-

eases have been classified in a standard fashion to enable the reader to locate information rapidly.

Infectious Diseases. The use of cortisone and ACTH in the infectious diseases is a controversial point[8,11]. Patients receiving these agents may develop serious infections without the usual signs and symptoms, and in some, infection may not even be suspected before autopsy. There is no doubt that, at least temporarily, fever is decreased and patients feel better. On the other hand, it is equally certain that there is no action upon the infecting organism, nor is there bolstering of the defense mechanism of the host. In animals, the outcome may be unaltered, or mortality increased[12].

The issue that remains undecided is whether changing the response to the infecting organism is good or bad for the patient; whether the temporary increase in comfort is obtained only at the cost of increased complications and mortality. For the most part, the evidence in humans is inconclusive, and it is not possible at this time to make a decision. The prostration and collapse accompanying acute virulent infection is interpreted by some as adrenal cortical failure. Since a temporary increase in strength may keep the patient alive until specific antibiotic therapy can be effective, some workers conclude that cortisone or ACTH is mandatory in desperate infections[3]. Certainly, where there is failure of the adrenal cortex, as in fulminating meningococcal sepsis (Waterhouse-Friderichsen syndrome), cortisone added to chemotherapy has been a life saving measure[16].

There is reasonably secure evidence that these agents are valuable in typhoid fever (patients treated with cortisone and chloramphenicol recovered more rapidly than those treated with chloramphenicol alone; improved nutrition was a prominent feature)[17], trichinosis (fever and muscle pain during the several weeks of invasion and dissemination were greatly relieved)[15], and encephalomyelitis complicating anti-rabies immunization (there was recovery from fever, confusion, and headache)[9].

In tuberculosis the decreased tissue reaction might, in some cases, be advantageous, but the lowered cellular defense is always dangerous. There is evidence of activation of tuberculosis in patients receiving these agents for other conditions[13]. This danger prohibits their use in controlling the acute manifestations of tuberculosis, though, with further experience, they may prove to be valuable in special states like laryngeal tuberculosis[14].

They have no value in streptococcal infections, nor have they reduced the incidence of post-streptococcal complications[10]. Their use in rheumatic fever presents a special problem.

Rheumatic Fever. The effect of cortisone and ACTH on rheumatic fever may be the most significant therapeutic advance contributed by these hormones[18,19,23,24]. In patients with acute rheumatic fever there is rapid return of the temperature to normal, an increase in appetite and in feeling of well being, and disappearance of joint pains. Symptomatic relief of this nature, however, can be provided by more economical treatment. The decisive question is whether cortisone and ACTH prevent or decrease damage to the heart. There is the fact that the subcutaneous nodules of rheumatic fever generally soften, shrink, and disappear, indicating that rheumatic lesions of the type found in the myocardium can be affected by these hormones. When acute rheumatic fever is treated early in its course, there is direct evidence of improvement of the myocarditis. Tachycardia decreases

gallop rhythm disappears, and the prolonged P-R interval returns to normal. Congestive heart failure is abolished in the vast majority of cases. (Sodium and water retention may make the failure worse at first, but it can be controlled by diuretic agents and low sodium intake.)

Pericarditis, with or without effusion, almost always disappears more rapidly than could be expected if recovery were spontaneous.

Controversy continues over the effect cortisone and ACTH may have on lesions of the endocardial surface of the valves. In the life history of rheumatic fever, these are most important, for they provide the site at which bacterial endocarditis may develop, or, as chronic valvular disease, they may lead to congestive failure. During the few years following an attack of rheumatic fever, murmurs are the only evidence we have of these lesions. Unfortunately, they are not conclusive evidence, for murmurs heard during the attack of rheumatic fever may not be indicative of the chronic proliferative lesions that damage valves, while some destructive lesions do not produce murmurs until years after the attack. Several investigators report that many murmurs heard in the attack of rheumatic fever disappear during treatment with ACTH or cortisone. In follow-up examinations many months later, these murmurs have not recurred[23,24]. It is hoped that cortisone and ACTH have suppressed the early exudative lesions of the valvular endocardium, and thus prevented the late proliferative destruction of valvular function. Other investigators believe murmurs that disappeared during treatment were only the transient murmurs of acute rheumatic fever, caused by cardiac enlargement or valvular edema; still others have not detected the disappearance of significant murmurs during treatment with these agents[21]. The most important question in relation to the use of cortisone and ACTH as therapeutic agents cannot be answered until years have elapsed, and the incidence of valvular disease in children now being treated with ACTH and cortisone can be compared to the incidence in children not so treated. Studies are under way to evaluate, by long-term follow-up, the results of cortisone and ACTH in the treatment of acute rheumatic fever. Meanwhile, on the evidence now available[18,23,24], it seems reasonable to administer cortisone and ACTH, as early as possible, to all patients with acute rheumatic fever, and in doses sufficient to suppress all the rheumatic manifestations.

There is lack of agreement over the effect of these agents on the natural course of rheumatic fever. Some think acute attacks treated with these agents are shorter than those in untreated patients[23]. The more persuasive evidence at the present time indicates that the natural course of the disease is not influenced, but only the rheumatic manifestations are suppressed[18,22].

Sydenham's chorea has been a difficult complication. In some patients it has disappeared in 1 or 2 weeks[23], while in others it has not been affected by the use of cortisone or ACTH.

Experience with these agents in active rheumatic fever of long duration has not been encouraging. The response of fever and systemic symptoms is less dramatic than in early acute rheumatic fever. Although tachycardia, P-R interval, and even congestive failure may improve during treatment, the majority of clinically active patients return to the pre-treatment status when the hormones are discontinued[20]. Murmurs known to have been present for a long time before the hormones are started do not disappear. Some of the

patients continue to deteriorate, and die from rheumatic fever despite treatment.

Diseases of Unproved Etiology. Sarcoidosis. There is symptomatic relief during treatment with cortisone or ACTH, especially in acute cases where low grade fever disappears and lassitude is replaced by a feeling of well-being[28]. There is regression of pathologic lesions. However, because of the tendency to relapse, the value of the hormones is established only where the clinical course is downhill, or in patients with incapacitating lesions in the lungs or the eyes. Patients with severe respiratory disability have been returned to normal living (lesions in the chest film cleared promptly) [25,27], and patients who were virtually blind from sarcoidosis of the eye have had restoration of vision to an adequate level[26].

Diseases of Allergy. The demonstration that cortisone and ACTH could provide relief in most of the common diseases of allergy was soon followed by abuse of these agents. The dramatic improvement led many physicians to put aside the established methods of treatment, resulting in unnecessary expense to the patients. Development of hypersensitivity to injected ACTH is an additional complication in some allergic patients.

Hay Fever. The distressing symptoms of seasonal or perennial hay fever are controlled by these hormones in many patients[34]. However, there must be exceptional circumstances to justify their use, either to provide relief during the short period of seasonal hay fever, or to produce temporary symptomatic improvement in perennial hay fever. Proper allergic management generally can accomplish more for the patient, with less hazard and less expense.

Asthma. Cortisone and ACTH can be counted on to relieve the symptoms of bronchial asthma, whether of the extrinsic or intrinsic variety[29,31,32,33,35]. In those cases in which the period of relief induced by the hormonal agents can be combined with identification and removal of the allergic cause, the remission of asthmatic symptoms persists after treatment is stopped. When the allergen is still present, or the asthma is intrinsic, cessation of hormonal therapy is followed by return of asthmatic symptoms. The present-day management of asthmatic patients is advanced at 2 points. First, status asthmaticus is consistently interrupted; secondly, a temporary respite in chronic bronchial asthma may permit improvement in nutrition, or provide opportunity for the patient to carry out a necessary activity of short duration. It is interesting to note that many patients are not completely relieved of their asthmatic symptoms, but that treatment with these agents makes them more responsive to the ordinary bronchodilators[35].

Drug Hypersensitivity and Serum Sickness. Fever, skin lesions, and joint symptoms are well controlled by cortisone or ACTH[30]. Since these are self-limited conditions, the hormones can maintain patients free of discomfort while they run their natural course.

Diseases of Collagen. Cortisone and ACTH have provided the first effective methods for treating these diseases; while they are not ideal, control of the disease process is a remarkable achievement. Two diseases sometimes classified with the collagen group are considered elsewhere, rheumatic fever in the section on Infectious Diseases and rheumatoid arthritis in the section on Diseases of the Joints. Two recent reviews discuss the use of these hormones in collagen diseases[38,42].

DISSEMINATED LUPUS ERYTHEMATOSUS. There is prompt improvement in systemic manifestations in patients treated with ACTH or cortisone. Fever and joint pain disappear early, patients feel well, and appetite improves. Effusions gradually clear, and the pericardial friction rub disappears. Skin lesions fade in a few weeks. The initial response is dependable, and has been demonstrated in patients who were thought to be moribund. Rarely was there improvement in cerebral, cardiac, or renal dysfunctions present at the time treatment was begun.

It has been unusual for a remission induced by these agents to persist after they are discontinued. Relapses generally respond to a second course, but some investigators continue treatment, lowering dosage to find the most economical maintenance level[39]. Many of the patients in whom dramatic early results were described have since died[36]. Cortisone or ACTH controls the acute manifestations of disseminated lupus, and may be life-saving in critical periods; if given early they may prevent progression of the disease process, but have no effect on damage already done[40,46].

PERIARTERITIS NODOSA AND CRANIAL ARTERITIS. The hormones interrupt the active, progressive stage, controlling fever, pain, and other symptoms, and permitting the arterial lesions to heal[37,41,45]. On cessation of treatment, relapse is the rule, but there is promise of managing this fatal disease by continuous maintenance therapy[43]. It is of utmost importance that the agent be used early and in high doses, before widespread damage has occurred. Not only is the loss of renal or cerebral function permanent, but healing of the arterial lesions by a fibrous process may further impair the circulation of these vital organs. In several patients the latter factor was the cause of death after the active disease was controlled.

DERMATOMYOSITIS. In the acute fulminating form, generally fatal, ACTH has proved life-saving, and has induced remissions lasting many months. In the chronic form, with atrophy of the skin and replacement of muscles by fibrous tissue, the slight improvement noted during ACTH has usually been temporary[47,48].

SCLERODERMA. When these agents are given early in the course of the disease, symptoms may be partially controlled. There is danger in their use and, as in periarteritis nodosa, improvement followed by untimely death has been reported[44].

Diseases Due to Chemical Agents. From preliminary reports, there is reason to believe that these agents may provide a smoother withdrawal period in the treatment of addiction to narcotics or barbiturates[49,51]. In chronic alcoholics, rapid recovery from delirium tremens has been reported[52]. Dramatic relief of pain and of local edema, produced by ACTH, have been reported in a patient bitten by a black widow spider, and in one bitten by a copperhead snake. The hormones appear to be of great value in the treatment of poisoning by animal venom[50].

Diseases of Metabolism. GOUT. Rapid relief of pain and inflammation is the usual result of treatment of attacks of acute gouty arthritis with cortisone or ACTH. The "flare-up" that occurs when the hormones are discontinued has been prevented by simultaneous administration of colchicine[53,54].

HYPOGLYCEMIA. The action of cortisone and ACTH on carbohydrate metabolism provides a method of maintaining the blood sugar of patients with hypoglycemia, but in only a few does it improve significantly on the present management[55].

Neoplastic Diseases. ACTH and cortisone have shown 2 valuable actions

in the neoplastic diseases: First, they induce temporary remissions in many of the lymphomata, and second, they may aid in the management of difficult problems by influencing the secondary manifestations of the malignant diseases. The early promise of real advance, offered by encouraging results from animal experiments, has not been fulfilled. Patients with melanoma, carcinoma, and sarcoma originating in various sites, and at various stages of invasion, have been treated with ACTH or cortisone, but no measurable effect on tumor growth has been observed. There was often temporary improvement in the general condition, due to the non-specific action of the hormones, with increase in appetite and in the feeling of well-being, and decrease in pain, fever, and inflammatory edema. Occasionally, the decrease of inflammatory edema is valuable, as, for example, when it involves the trachea or bronchi and causes respiratory difficulty[62]. However gratifying the temporary improvement, the use of these agents brings financial burden, hazard from the side effects, and damaging psychological sequelae for patient and family when the temporary improvement does not continue. There is no evidence that they prolong life, and the opinion is, rather, that they shorten it, for some of the carcinomas appear to grow faster during and after treatment. In addition, a number of patients who died while under treatment were found at autopsy to have multiple abscesses and terminal infection which was not discovered during life[63].

ACTH and cortisone appear to be of real value in the treatment of acute leukemia in childhood[58,60], particularly when combined with the folic acid antagonists[57]. Temporary remissions, lasting from one week to many months, are induced in somewhat over half of the patients. Most of these will respond to a second or third course before refractoriness develops. There seems to be no relation between refractoriness to these agents and to the folic acid antagonists; many of the patients who do not respond to the hormones respond to folic acid antagonists, and vice versa. The effect of these agents in adults with acute leukemia has been less dramatic, and it has frequently been felt that the disease is augmented in patients who fail to respond. Some remissions, however, have been induced in acute lymphatic leukemia. The majority of the patients with chronic lymphatic leukemia, lymphosarcoma, and Hodgkin's disease respond to these agents by a temporary remission in the clinical status, with regression of the lesions[59]. Since the remissions are rarely superior to those induced by Roentgen-ray or nitrogen mustard, ACTH and cortisone have been abandoned in some institutions[61]. In a few patients with multiple myeloma, temporary improvement in clinical status and relief of bone pain have followed treatment with ACTH or cortisone[56].

Diseases of the Digestive System. Ulcerative Colitis. ACTH induces remissions in most patients with ulcerative colitis[70,72]. There are ordinarily a reduction in the diarrhea, relief of abdominal pain, fall in temperature, and increase in appetite followed by gain in weight. Although sigmoidoscopic examination reveals that the ulcers persist, there is reduction in the inflammatory reaction and the mucosa is more pliable. The most satisfactory remissions occur in patients who have severe systemic symptoms of short duration. The failures have been among patients who have had ulcerative colitis for many years, and have fibrosis and other structural changes in the intes-

tine[69]. Cortisone is much less effective than ACTH.

In about one-half the patients, relapse follows immediately when ACTH is terminated. In the others, there is a variable period of remission, some lasting several years. There have been attempts to control the disease over a long period by continuous maintenance doses of ACTH, or by repeated courses; the most satisfactory method is not yet known[74]. It is generally concluded that ACTH is a valuable addition to other methods of therapy for ulcerative colitis, particularly in producing remissions in the early stages of the disease, and is an important aid in preparing patients for ileostomy.

Regional Ileitis. This disease responds to ACTH in the same fashion as does ulcerative colitis[70].

Idiopathic Steatorrhea (nontropical sprue). Improvement has been seen during treatment with ACTH or cortisone[64,65,75], with disappearance of diarrhea, increased sense of well-being, improved appetite and gain in weight in patients who were resistant to the usual methods of treatment.

Peptic Ulcer. There have been a number of cases of perforation of peptic ulcer reported during therapy with these hormones, not only in patients with a history of peptic ulcer, but in patients who have never given any indication of gastrointestinal disease[71,77]. Masking of the symptoms of peritonitis makes the diagnosis difficult[66].

Liver Disease. When ACTH or cortisone is used to treat liver disease, the patient becomes alert and cooperative, feels much better, and the appetite returns, encouraging him to eat the unpalatable diet thought to be advantageous. In the case of chronic liver disease, such as portal cirrhosis, the disease process is not influenced, and only rarely does the temporary boost justify the use of the hormones[67,73].

However, in the acute liver diseases, infectious hepatitis[68] and homologous serum hepatitis[76], the relief of symptoms is of practical importance. The cooperative, hungry patient is able to protect his liver by an adequate diet. On several occasions, the hormones stopped a disease process that was, to all appearances, proceeding to liver death. However, other patients died, although they received treatment. In spite of the fact that liver function and liver size progress toward normal faster than in patients not given ACTH or cortisone, the disease process is not altered, and relapses occur regularly when treatment is discontinued too soon. The effect that treatment of acute liver disease by these agents might have on the later development of chronic liver disease has not been established.

Diseases of the Lungs. There have been reports of improved respiratory function following cortisone or ACTH, but in most of these, pulmonary symptoms were caused by a systemic disease, such as bronchial asthma or sarcoidosis. A few cases of emphysema and of chronic pulmonary fibrosis have shown a temporary decrease in dyspnea and cough, but rarely does the possibility of transient slight improvement justify treatment with these hormones. Indeed, some patients with emphysema deteriorate under treatment, possibly due to congestive failure[78]. The use of cortisone and ACTH in the ordinary forms of silicosis has not been properly assessed, but at least in the granuloma following inhalation of beryllium there has been consistent improvement in respiratory function during treatment[80]. Partial clearing of the lesions as seen in the roentgenogram suggests these agents may play an important role in

the management of beryllium granulomatosis. The symptoms of allergic pneumonia (Loeffler's syndrome) have been controlled[79].

Diseases of the Kidneys. There is little evidence that ACTH or cortisone influences the course of acute or chronic glomerulonephritis, despite occasional temporary changes in urinary findings or on blood analysis[86]. The improvement seen in a few patients may represent natural remissions in the course of the disease. As yet no data are available to indicate whether ACTH or cortisone decreases the kidney damage secondary to inflammation.

Nephrotic Syndrome. One of the more satisfactory methods of inducing diuresis in the edematous stage of the nephrotic syndrome has been treatment with ACTH[81,82,83,84,85]. In well over three-fourths of the patients in whom a short course was tried, there was substantial diuresis during the week following abrupt withdrawal of the hormone. It occurred whether the nephrosis was on the basis of glomerulonephritis or diagnosed as true nephrosis. In many of the patients edema cleared completely. Although almost all the patients began reaccumulating edema within several months, the diuresis, associated with lessening of biochemical defects and improvement in kidney function, was helpful in the management of these patients. Repeated courses are usually successful in re-initiating diuresis. The data published up to the present time indicate that ACTH is far more effective than cortisone.

There are a few reports in the literature describing cases in which active progressive lesions were arrested, apparently by repeated diuresis with ACTH. On the other hand, there is the fact that a number of patients with the nephrotic syndrome failed to obtain diuresis or to show any evidence of improvement, and that some patients with glomerulonephritis have passed through the nephrotic stage to death in renal failure even though treated with ACTH.

Diseases of the Blood. Although ACTH and cortisone produce beneficial results in many diseases of the blood, in most of these other therapeutic measures are more satisfactory[95]. Reversal of the anemia and leukopenia secondary to diseases of collagen, or to lymphoma, is a striking feature of treatment with the hormones.

Acquired Hemolytic Anemia. Patients with acquired hemolytic anemia, either idiopathic or secondary to lymphoma, have improved as a result of intensive treatment with ACTH or cortisone[88,93]. Within a few days the demonstrable agglutinin activity declined, followed by progressive clinical improvement with rising red cell count and hemoglobin. Icterus disappeared, and the survival time of transfused erythrocytes returned almost to normal. Relapse occurred at varying intervals following the discontinuation of the hormones. Oral cortisone has been effective for maintenance. Continued administration may in some cases lead to exhaustion of the mechanism that produces abnormal agglutinin and thus control the disease. Another approach is to reduce the abnormal antibody by using the hormones and to follow them by splenectomy or nitrogen mustard treatment.

Aplastic Anemia. The majority of patients have not been improved, but in several there has been remarkable response. Blood cells were again formed; the need for transfusion was sharply reduced and in some cases eliminated, as long as the patient continued to receive ACTH or cortisone[90]. There is no explanation for the fact that a few patients with hypoplastic

anemia will form blood cells when given cortisone or ACTH. Even in those who respond, continuous treatment with the hormones may offer no advantage over repeated transfusions.

COOLEY'S ANEMIA. In about half the patients there is temporary stabilization of the red count and hemoglobin, with less need for transfusions, during treatment with ACTH[94].

IDIOPATHIC THROMBOCYTOPENIC PURPURA. In the majority of patients a remission in the purpura is induced by cortisone or ACTH[87,89]. In some, particularly those who have not had splenectomies, the remission continued after therapy was stopped. In others, the purpura recurred, but the patients could be kept in a purpura-free state by continuous maintenance. Allergic purpura is promptly cleared by these agents[91].

AGRANULOCYTOSIS. The return of white blood cells appears to be enhanced and more rapid with ACTH therapy[92] than by other agents.

Diseases of the Cardiovascular System. There has been no convincing evidence that cortisone or ACTH is of value in the management of cardiovascular disease. There are many reports of congestive failure precipitated by the hormones in patients with heart disease. Although the blood pressure in essential hypertension may decline slightly, no beneficial effects have been demonstrated[96]. Systemic diseases which involve the heart, notably rheumatic fever and disseminated lupus, are discussed in other sections of this report.

Diseases of the Ductless Glands. As might be expected, ACTH and cortisone provide valuable replacement therapy in a number of disorders of the ductless glands[101]. ACTH may be utilized to advantage in hypopituitarism[97,99]. Cortisone has reversed virilism in adrenogenital syndrome[102], and, combined with other adrenal factors, has provided additional security for patients with Addison's disease[98,101]. These hormones are often administered to the tired or psychoneurotic patient in the belief that he is suffering with functional adrenocortical insufficiency, without following the necessary procedures to establish proof. Thorn has discussed the diagnosis and treatment of this syndrome[100,101].

Diseases of the Joints. These diseases occupy a special place in any discussion of cortisone and ACTH, since the treatment of rheumatoid arthritis was the first demonstration of their remarkable ability to modify tissue response[1].

RHEUMATOID ARTHRITIS. The effects of cortisone and ACTH on patients with active rheumatoid arthritis are dramatic. There is disappearance of stiffness and weakness of the muscles, of tenderness and swelling of the joints. Temperature returns to normal, and appetite and feeling of well-being return. Flexion-contractures are usually diminished, but there is no effect on fibrotic contractures or on deformities of the articular cartilage or bone. Except for minor symptoms of short duration, this improvement is maintained throughout the period of treatment with these agents[109,112]. The clinical variants of rheumatoid arthritis (juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Reiter's disease) respond to cortisone and ACTH in a similar fashion.

The significance of potential reversibility of rheumatoid arthritis cannot be overestimated[108]. However, there are problems to be met before all patients can be returned to a normal, active life. When treatment with the hormones is discontinued, arthritis returns. The period before relapse may be only a few days, or it may last months. About one-quarter of the patients have a remission lasting one month or longer.

The emotional readjustment that accompanies relapse has been described as very painful[106]. There is no way of predicting which patients will have a relatively long remission after treatment[114], nor is it certain that the remissions are not natural ones, but have been induced by the hormones[107].

In view of the difficulties, cortisone and ACTH may serve best not as a routine treatment for rheumatoid arthritis, but in special cases to halt rapidly progressing disease, or to reach a clear objective in rehabilitation[106]. In regard to the future, research is under way in many institutions exploring the possibilities of continuous maintenance with cortisone[103], of supplementing cortisone with ACTH[1], or of combined use of cortisone and physical medicine[111], gold[110], or paraminobenzoic acid[113].

Degenerative Joint Disease. Although there are reports of decreased pain and increased range of motion in some patients, there has been no evidence to indicate that cortisone or ACTH is superior to conservative treatment of degenerative joint disease[104,105].

Diseases of the Muscles. The pain of many disorders of muscle and its accompanying structures, such as bursitis, fibrositis, and tendinitis is relieved by these agents. For the most part their use is not justified, but a fairly strong case has been made for trial in "shoulder-hand" syndrome (reflex dystrophy) and "frozen shoulder" (periarticular fibrositis), where pain relief and increased function often persist after the agents are discontinued[115].

Diseases of the Nervous System. There have been trials with these agents in small groups of patients with a variety of neurological disorders[117, 119].

Myasthenia Gravis. Weakness and malaise are increased during administration of a short course of ACTH, but when the drug is discontinued, the majority of patients have a partial remission with increased feeling of well-being and improved work performance on reduced neostigmine dosage[120]. The improvement increased for several months in some patients, while others returned toward the pretreatment level.

Epilepsy. There may be reduction in frequency of attacks, but the hormones offer no advantage over present anticonvulsant drugs[118].

Multiple Sclerosis. A few patients with spastic ataxic syndrome improved during therapy, but relapsed immediately after ACTH was stopped. There is the possibility, not yet established, that ACTH protects patients from further damage[117].

Psychiatric Disorders. Mood changes, particularly euphoric, have led to the trial of these agents in psychiatric disorders, but evidence of satisfactory results has not been published. A recent review considers the psychiatric viewpoint[116].

Diseases of the Skin. Several excellent review articles have appeared recently on the use of cortisone and ACTH in dermatology[123,125,127].

Pemphigus. After treatment of any of the common forms of pemphigus with these agents, new lesions no longer appear; the bullae and erosions improve and occasionally disappear[121,124]. Although only half the cases of pemphigus now recorded in the literature have been arrested, the rate of improvement may increase as large doses come into more general use. In most patients lesions begin reappearing several weeks after administration of the hormones is stopped. Repeated courses have generally been necessary within 2 or 3 months, and in the vast majority have again been effective. Occasionally remissions may last 8 months or longer. Although ACTH and cortisone have no permanent effect, they delay the fatal termination and

make the management of pemphigus less difficult.

EXFOLIATIVE DERMATITIS. The skin has almost always cleared with use of the hormones, but following the cessation of treatment, symptoms recur in most cases[130].

ACTH and cortisone are effective in a number of the acute, self-limiting diseases, and may be indicated for the control of serious discomfort[128,129]. Among these are urticaria, erythema nodosum, erythema multiforme, and severe contact dermatitis. Control of the acute "lepra reaction" by these hormones should be of great help in the chemotherapy of leprosy[126]. The pain during and after facial herpes zoster has been controlled without influencing the course of the cutaneous disease.

Many chronic diseases of the skin respond to ACTH and cortisone, but relapse soon after treatment ceases. Often relapse is worse than the original disease (rebound phenomenon)[122]. Psoriasis, atopic eczema or neurodermatitis, chronic discoid lupus, dermatitis herpetiformis, mycosis fungoides, and certain of the lichenified lesions should not be treated with ACTH or cortisone unless there is a special problem. Patients with these diseases have come to depend on cortisone so completely that they demand it with the ferocity seen in drug addicts.

Surgery. There have been numerous suggestions for the use of cortisone and ACTH in surgical diseases[133]. Most of these need confirmation. Relative adrenocortical deficiency may occur in post-operative patients and increase surgical mortality[134]. Of special interest is the role these agents might play in decreasing toxicity, improving nutrition, and hastening convalescence following severe burns[131,132]. Since they also delay healing and decrease resistance to infection, it will be some time before their role is clarified[135].

Obstetrics. Pregnant women are peculiarly resistant to the physiologic action of cortisone and ACTH. There is the observation in pregnant mice that cortisone produces congenital anomalies[139]. However, it is generally believed that a pregnant woman who has a disease in which the hormones are clearly indicated should be permitted to receive them.

PRE-ECLAMPSIA. In some reports there was relief of headache, clearing of the sensorium, and diuresis[136,141], while in others there was no beneficial effect[138,140]. Evidence of real advantage for these compounds is still lacking.

ERYTHROBLASTOSIS FETALIS. Use of these agents in Rh-negative women in the last months of pregnancy, and in erythroblastotic infants, may prove to be valuable in preventing destruction of blood cells and damage to vital organs[137,142].

Pediatrics. The special problems these agents present in children are discussed in recent reviews[143,144,145]. The sections of this report on rheumatic fever, kidney, skin, allergy, and neoplastic diseases are of interest.

Ophthalmology-Otolaryngology. The use of locally-applied cortisone and parenteral ACTH in eye disease is discussed in recent reviews[148,149]. These agents have revolutionized the management of acute non-specific inflammatory disease of all structures of the eye, and when given early, have been uniformly successful in providing relief and preventing ocular damage. The destructive reactions following trauma and in sympathetic ophthalmia have been lessened, allergic eye symptoms controlled, and some cases of chronic inflammatory disease improved.

A recent review in this journal indicated that cortisone and ACTH modify

a number of conditions seen by the otolaryngologist, but, except in allergic diseases, are not of special value[146]. Tracheotomy was avoided in several patients with laryngeal edema, but there must be further experience before cortisone is used in this manner[147].

Summary. The literature reporting the current use of cortisone and ACTH is examined and the diseases which are modified by these agents are reviewed in this report. The nature of the modification is described in each case so that the reader, faced with a difficult therapeutic problem, may determine whether a worthwhile result is likely to follow trial of these agents.

Matters of dosage, mode and duration of administration will be found in the original articles here reviewed, to which the reader is referred.

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RADIOLOGY

UNDER THE CHARGE OF

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GENERALIZED DECREASED BONE DENSITY

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THE roentgenologist feels very much at home in the study of bone disease. He possesses a powerful tool in the form of the Roentgen ray which penetrates matter with a readiness inversely proportional to density, thickness, and atomic number. The density of normal bone is moderately greater than that of the surrounding soft tissues. Calcium is a major ingredient of bone and since it has an atomic number of 20, bone has a higher average atomic number than the soft tissues. Both of these factors, increased density and increased atomic number, endow bone with the ability to absorb Roentgen rays greater than surrounding tissues.

For many years scientists of different disciplines have been studying the composition and crystalline state of bone salts. Recently Hendricks and Hill[10] have proposed a hypothesis which at least resolves many conflicting data. They postulate that bone salts crystallize as hydroxyapatite. As the crystals grow they are surrounded by many extraneous ions including carbonate, magnesium hydroxide, citrate and sodium ions. These ions, together with ionized calcium and phosphate, cover the surface and eventually stop crystalline growth. A new surface may be started separately by the formation of a new crystal or by covering up the old one. In either event the extraneous surface ions are retained external to the crystalline lattice. Bone is an example in which separate crystalline formation occurs. In enamel old crystalline surfaces may be covered by new hydroxyapatite crystals.

ROENTGEN ANATOMY OF BONE[22]. For purposes of Roentgen analysis a typical long bone may be divided into the diaphysis or shaft, the metaphyses or the ends of the shaft (in the immature bone these are the actively growing portions), and the epiphysis, which is formed from cartilage and usually enters into joint formation. The term "modeling" is applied to the general process of shaping the diaphysis. A thin, constricted shaft would be "overmodeled."

Further analysis would divide the bone into a compact outer shell, the cortex, and the inner spongy or cancellous bone. The marrow cavity is centrally placed. Both the periosteum and endosteum are fibrous sheets encasing the outer and inner aspects respectively of the cortex. They cannot

be visualized directly on the roentgenogram. However, inferences can be drawn concerning them by noting adjacent cortical structure.

The finest structure which can be seen on the roentgenogram is the trabecular pattern. Certain authorities[12] term the primary trabeculae as those which run parallel to the lines of stress. They generally lie parallel to the long axis of the bone. The secondary trabeculae are the cross-struts and do not run parallel to the line of stress. The trabecular structure is governed by the principles of Wolff's law to a great extent which means that bone has a tendency to form where the lines of stress are in greatest concentration.

It should be realized that bones are not the inert, dense, white permanent structures frequently associated with a fixed skeleton. They are composed of living, metabolizing tissues sensitive to innumerable environmental influences and in delicate balance with the homeostatic mechanisms of the body. Furthermore, any viable bone is constantly and simultaneously building up and tearing down, regenerating and degenerating. Osteogenesis is the anabolic process and osteoclasis or resorption is the catabolic process. In the normal adult the rates are for practical purposes equal.

Recognition of Decreased Bone Density. Decreased bone density on the roentgenogram, either locally or generally, can be translated in physicochemical terms into decreased hydroxyapatite in the bone tissue. The roentgenologist intuitively notes any gross deviation from the normal. Often localized areas of decreased bone density are easier to perceive than the generalized decreased bone density. Local lesions stand out in contrast to normal surrounding bone, whereas generalized decreased bone density can only be seen in contrast to the surrounding soft tissue. The changes may be so subtle that often a fair degree of diminished bone density is ascribed to technical factors. In order to refine the Roentgen appreciation of demineralization several investigators proposed photodensitometric systems which attempt to quantitate the relationship between film density and the concentration of calcium salts[8,11].

Causes of Decreased Bone Density. The causes of decreased bone density or diminution in the amount of calcium salt in bone can be divided into 2 basic disease processes: 1) those diseases giving rise to a disturbance of mineral metabolism, and 2) those diseases primarily causing a disturbance in development of the organic component of bone, the osteoid tissue. The diseases which cause a disturbance of mineral metabolism can be grouped in the generic category of malacic bone disease. Those diseases which cause a disturbance of the organic components of bone can be grouped in the generic category of porotic bone disease. The malacic diseases are rickets, osteomalacia, osteonephropathy, hyperparathyroidism and idiopathic hypercalciuria. The porotic bone diseases[2] are disuse atrophy, scurvy, osteogenesis imperfecta, Cushing's syndrome, senile osteoporosis, postmenopausal osteoporosis and hyperthyroidism.

Malacia. The malacic bone, which lacks calcium salts but has an adequate osteoid matrix, is softer, more flexible, more pliable, and generally lacks the rigidity associated with the normal skeletal structures. Any influence which deprives or depletes the bone of calcium phosphate without interference with osteoid production would tend to produce bone malacia. Primary influences are inadequate calcium or phosphate ions, a lowered serum bicarbonate or CO_2 combining power, and an

over-production of parathyroid hormone.

The factors which tend to reduce available calcium or phosphate ions may be nutritional, such as a low intake of calcium, phosphate or Vitamin D. Insufficient exposure to ultraviolet light decreases the amount of available Vitamin D in the body. A borderline case of barely sufficient intake of minerals or Vitamin D may be thrown into a deficiency status by stress demands on the body, such as pregnancy and lactation[19].

Disturbances of the small bowel in which fats are inadequately absorbed will tend to cause loss of the fat soluble vitamins, including Vitamin D. The calcium also tends to combine with fatty acids and form calcium soaps which are excreted from the colon. Examples of gastrointestinal disorders which tend to produce malacia are sprue, celiac disease, biliary stenosis, pancreatitis, and inadvertent surgical errors such as a gastroileostomy. A physiological defect of the intestinal epithelium, in which it is unable to absorb normal doses of Vitamin D, produces what is called refractory rickets, sometimes known as late rickets or rachitis tarda.

The excessive retention of acids reflected in a low carbon dioxide serum combining power, or excessive excretion of calcium or phosphate due to deranged renal function will encourage the development of malacia. The various types of osteonephropathy would fit into this category.

Over-production of parathyroid hormone, either by hyperplasia, adenoma, or rarely carcinoma, secondarily increases the urinary excretion of phosphate. Subsequent to this phosphate diuresis the blood calcium rises, which in turn causes an increased loss of calcium in the urine. There is also

Chart 1.

BONE MALACIA

A. NUTRITIONAL
  1. Vitamin D lack—Rickets
  2. Mineral and Vitamin D lack—Osteomalacia
  3. Vitamin D resistant—Refractory rickets
  4. Gastrointestinal tract disease
    a) Steatorrhea
      1. Celiac disease
      2. Sprue
      3. Pancreatitis, rarely carcinoma of the pancreas
      4. Biliary stenosis or atresia
    b) Short-circuiting operations
      1. Inadvertent gastro-ileostomy

B. RENAL DISEASE
  1. Glomerular osteonephropathy
    a) "Renal rickets" (renal dwarfism, renal osteodystrophy)
      1. Due to chronic nephritis, polycystic kidneys, pyelonephritis, congenital obstructions of the bladder neck, bands, valves, and others.
  2. Tubular osteonephropathy
    a) Renal acidosis—lack of ammonia formation
    b) De Toni Fanconi Syndrome—Amine diabetes, failure to absorb certain amino acids including cysteine, phosphates, and glucose. Considered to be a proximal tubular defect.

C. ENDOCRINE
  1. Hyperparathyroidism

some evidence that the parathyroid hormone has a local, direct, lytic reaction on bone[3,4].

Many of the above factors are interrelated and often several act in a concerted manner in a given case of manifest malacic bone disease. For example, in hyperparathyroidism a low dietary intake of calcium, a high output of parathyroid hormone, and renal insufficiency due to calculi may act together to produce a striking decrease in the bone density. The following is a chart of diseases producing bone malacia.

It must be emphasized that subclinical and subradiologic forms of diseases tending to produce bone malacia exist. The clinical disease is usually full blown before radiologic manifestations occur. Hyperparathyroidism is an excellent case in point. Frequently the disease exists without either radiologic or histologic abnormalities. Some authors retain the term osteitis fibrosa cystica or osteitis fibrosa generalisata to indicate hyperparathyroidism with bone involvement. Primary hyperparathyroidism can exist in four forms. The percentages appended use as a basis the 64 proven cases of primary hyperparathyroidism of The Massachusetts General Hospital series.

1) Osteitis fibrosa generalisata with renal lithiasis or calcinosis—17%.
2) Osteitis fibrosa generalisata without kidney disease—37%.
3) No bone disease but renal lithiasis or calcinosis—46%.
4) No bone disease or kidney disease—approximately 1%.

Albright *et al.*[1] claim that about 5% of all cases who have kidney stones have primary hyperparathyroidism.

It will be noted that hyperparathyroidism is included in the malacic bone diseases. One should not assume that it is identical with the specific entities called osteomalacia or adult rickets. There are certain similarities and many differences between hyperparathyroidism and osteomalacia. Both diseases, hyperparathyroidism and osteomalacia, are disturbances of mineral metabolism. In both the bones are soft and easily deformed. The trabecular pattern is coarse and the lamina dura is frequently absent. Some of the points of differences are the following. In osteomalacia the difficulty is in calcifying osteoid tissue, whereas in hyperparathyroidism there is an increased resorption of calcium salts from the bone. Osteomalacia shows increased amounts of osteoid tissue, whereas in hyperparathyroidism there is a marked increase in the number of osteoclasts as well as the precursor of osteoid tissue, the fibroblasts. Subperiosteal resorption and cyst formation or pseudocyst formation are striking features of hyperparathyroidism[18]. Chemically the serum calcium in hyperparathyroidism is generally high and that in osteomalacia is either normal or low.

The following is a chart of the Roentgen findings which are common to the malacic group to a greater or lesser degree.

Points of Differential Diagnosis. There are many similarities between hyperparathyroidism and glomerular osteonephropathy, otherwise known as "renal rickets" or renal osteodystrophy. Most authorities[1,9] agree that the bone changes in glomerular osteonephropathy are due to secondary hyperparathyroidism induced presumably by the high blood phosphate. Both hyperparathyroidism and glomerular osteonephropathy have in common the cotton-woolly appearance of the skull, the absence of the lamina dura, and subperiosteal bone resorption, especially affecting the middle phalanges. Hyperparathyroidism more frequently than glomerular osteonephropathy exhibits

cysts and pseudocysts in the bone. Pathologically the pseudocysts have considerable fibrous tissue and many osteoclasts. They are frequently confused with primary bone tumors, particularly giant cell tumors. Glomerular osteonephropathy occasionally is associated with small cysts, but, as a rule, the longevity of the patient is limited and the cysts are not well developed. The resorption of the bone at the margins of the sacroiliac joint causes an indistinct articular surface which resembles that of rheumatoid arthritis. The metaphyseal changes in glomerular osteonephropathy cannot be differentiated from Vitamin D-lack rickets. Both hyperparathyroidism and glomerular osteonephropathy frequently exhibit calcification in the media of the arteries and in the periarticular tissues. Patients with long standing glomerular osteonephropathy are frequently dwarfed[21] and have been referred to as renal dwarfs.

Chart 2.

MALACIC GROUP

A. ROENTGEN FINDINGS
1. *General appearance of bone*
   a) Coarse decreased density, "fibrous effect" due to thin, irregular porous cortex with resorption of secondary trabeculae. Thickened and poorly defined primary trabeculae. Indistinct, fuzzy appearance.
2. *Plasticity and reaction to trauma and stress*
   a) Softening, bowing—decreased stature, protrusio acetabuli, kyphosis, lordosis, Otto's pelvis, platybasia, "fish vertebra", flat pelves.
   b) The Milkman-Looser zones—symmetrical pseudofractures
   c) Greenstick fractures.
3. *Osteoid, fibrous and osteoclastic overgrowth*
   a) Pseudocysts due to osteoclasts and fibrous tissue. Usually calcify on healing.
   b) True cysts—usually fluid filled. Do not calcify on healing.
4. *Subperiosteal resorption*
   a) Cortical erosion forming a palisade like lacework frequently seen in the midphalanges, but may be seen elsewhere.
   b) Resorption of ungual tufts.
5. *Skull*
   a) Coarse resorption of inner and outer tables producing a mottled effect. A cotton-woolly effect produced by a retention of islands of normal bone density. Thickening of calvarium. Rarely cysts form.
6. *Lamina dura*—cortical bone adjacent to the periodontal membrane of the teeth.
   a) Diminished or absent.

B. CHANGES DURING ACTIVE GROWTH[15]
1. *Metaphysis*
   a) Calcified plate disappears.
   b) Radiolucent zone widened between metaphysis and epiphysis.
   c) Cupping, fraying, and widening of metaphysis.
   d) "Rosary" formed at the costochondral junction.
2. *Epiphysis*
   a) Cortex ill defined
   b) Spongiosa coarse
   c) Small or absent ossific centers

In osteomalacia symmetrical pseudofractures are frequently seen. These are the so-called Milkman[14]-Looser[13] zones. Albright claims this phenomenon is pathognomonic of osteomalacia, but other authorities[6] disagree. The Milkman-Looser zones may occur with-

out visible generalized decreased bone density. They usually are perpendicular to the primary trabeculae and are seen as radiolucent ribbons at right angles to the cortex. Pathologically osteoid tissue is present, but it is not calcified. The zones are most frequently seen in the axillary borders of the scapulae just below the glenoid process. They are also seen in the femoral necks, the ischial and pubic rami, the ribs, and metatarsals.

Note that the most characteristic chemical finding in this group is the increased serum alkaline phosphatase reflecting an increased osteoblastic activity. Malacic bone disease with a high nonprotein nitrogen and a high serum phosphate usually indicates glomerular osteonephropathy. The de Toni-Fanconi syndrome, sometimes referred to as amine diabetes, shows a high amino acid content in the urine. Occasionally a variant of this disease

Table 1.

CHEMICAL FINDINGS IN MALACIC BONE DISEASE

	Blood			Urine		Feces	
	Ca	Po_4	Ptase	Ca	PO_4	Ca	Comments
Osteomalacia rickets—Vit. D lack	°N-D	ND	•I	D	D	I	
Glomerular Osteonephropathy	D-N	I	I	D	D	N	Blood high urea PO_4 Acidosis, high Cl. Low CO_2.
Renal Acidosis	D-N	D	I	I	D	N	Normal blood urea. High Cl. Low CO_2.
de Toni Fanconi Syndrome	N-D	N-D	I	I	I	N	Urine-glucose increased. Amino acid, PO_4 increased.
Hyperparathyroidism	I	D	I	I	I	N	
Idiopathic Calciuria	N-D	N	I	I	D	N	

•N—normal
• D—decreased
• I—increased

In rickets, osteomalacia due to Vitamin D lack and in the malacias due to some aberration of the gastrointestinal tract, renal lithiasis or nephrocalcinosis is very rarely encountered. In osteonephropathy and hyperparathyroidism either renal lithiasis or nephrocalcinosis is quite frequently found.

The chemical findings in malacic bone disease can be summarized on the basis of the following chart. These findings may be of aid in the differential diagnosis.

is called cysteinosis because of crystals of the amino acid cysteine found in the reticulo-endothelial system. The de Toni-Fanconi syndrome characteristically shows an increased urinary phosphate and glucose[20]. The blood glucose and phosphate are not elevated. High serum and urinary calcium and low serum phosphate determinations with a high phosphatase usually indicate hyperparathyroidism. High urinary calcium with normal or

decreased serum calcium is found in idiopathic hypercalciuria.

Porotic Bone Disease. Diseases primarily due to a disturbance in the organic component of bone result in osteoporosis. The osteoid tissue which is composed of osteoblasts, collagen fibers, and interfibrillary material form a matrix upon which calcium salts are deposited. This component of bone is poorly understood. Only within recent years have intensive analytic studies been attempted on osteoid tissue. Electron microscopy has revealed collagenous fibers presumably produced by osteoblasts or from its products. These fibers are cross banded with a spacing of 640 Angstroms. Chemically mucopolysaccharides, certain amino acids, and hyaluronic acid have been demonstrated. It is believed that this component of bone is a fertile subject for research despite great technical difficulties.

The porotic bone is generally diminished in density not from a lack of available mineral salts but because the organic matrix is deficient. Either the matrix cannot be formed or it is being destroyed. Certain authorities consider the bone matrix to be only the interfibrillary material and exclude the osteoblasts, osteocytes and collagen fibers. Others believe the matrix includes interfibrillary material and collagen fiber, excluding only the cells.

Porotic bones exhibit decreased density. They also lack the elasticity and tensile strength endowed by normal osteoid tissue. They are consequently brittle and sustain fractures and infractions when subjected to relatively minor stress situations. Fractures generally heal slowly. The trabecular struc-

Chart 3.

CAUSES OF BONE POROSIS

(Abnormality in Osteoid Metabolism)

1. *Congenital*
   a) Osteogenesis imperfecta
2. *Lack of stress and strain*
   a) Atrophy of disuse
3. *Endocrine*
   a) Estrogen lack
      1. Post menopausal state
      2. Congenital hypoestrinism: ovarian agenesis
   b) Androgen lack
      1. Eunuchoidism
   c) Cushing's Syndrome
   d) "Alarm" reaction
   e) Hyperthyroidism
   f) Hypothyroidism
   g) Acromegaly
   h) Simmond's disease
4. *Nutritional*
   a) Vitamin C deficiency
      1. Scurvy
   b) Malnutrition
      1. Starvation, wasting disease
5. *Degenerative*
   a) Senile osteoporosis
6. *Unknown*

ture is fine and uniformly thin. The cortex is thin but has a distinct, sharp margin. The following chart of the causes of osteoporosis has been modified from Albright and Reifenstein[1].

Radiologic Findings in Generalized Bone Poroses. The radiologic findings in generalized bone poroses are not striking. However, certain features, especially in well advanced cases, are distinctive. The bone trabeculae become very fine and thin, developing a "washed out" appearance. Both the primary and secondary trabeculae are equally involved. There is no coarsening of the primary trabeculae with greater involvement of the secondary trabeculae such as is found in the malacic group. The marrow cavity of the bone is uniformly and subtly widened at the expense of cortical bone. This process takes place more on the endosteal side of the cortex.

The cortex becomes quite thin. Frequently it appears as a thin white line, the so-called "penciling effect". As the cortex approaches the ends of the diaphysis it becomes parchment-thin. Despite the thinness of the cortex, its periosteal side is sharp and well demarcated even though it is more radiolucent than the normal. In contrast to the sharp, thin cortex of osteoporosis, the malacic group of bone diseases has a fuzzy, poorly demarcated cortex. The bones in porosis are brittle and fractures are quite common. The fractures usually are complete, and not of the greenstick variety.

The spine shows changes which ordinarily cannot be differentiated from the malacic group. Due to the soft tissue overlay and the radiolucency of the vertebrae, the trabecular pattern cannot be visualized well enough for thorough analysis. Earliest stress changes are recognized when Schmorl's nodes are present. These nodes are quite common, even in normal individuals. They represent herniation of the nucleus pulposus through the end plate of the vertebral body. Various degrees of compression fractures, particularly near the lower thoracic and upper lumbar vertebrae, are seen. As the disease progresses the stature of the vertebral bodies is reduced and the intervertebral disc widens. The discs may become thicker than the vertebral body itself. Usually before this occurs the nucleus pulposus swells considerably and expands the central portion of the disc into the vertebral end plates. This process results in the so-called "codfish" vertebrae, in which the vertebral body is shaped into a biconcave disc.

The pelvis in generalized porosis is preferentially involved, as is the spine. The skull is less often involved and the extremities are usually spared. The lamina dura, if the patient is not edentulous, can be seen clearly. Renal stones, as in some of the malacic diseases, can form.

Osteogenesis Imperfecta. Osteogenesis imperfecta exhibits certain unusual and rather characteristic Roentgen findings. The bones are extremely brittle and numerous fractures occur with a minimum of stress. These fractures heal rather promptly. However, severe deformity of the limbs is often observed due to poor alignment. The shaft, besides being decreased in density, is quite slender. Because relatively normal endochondral bone formation takes place, there is no lack of linear growth in the long bones.

The skull is thin, particularly involving the cranial vault. Numerous wormian bones are visualized near the lambdoid suture. The skull in the patients who survive childhood usually shows a peculiar triangular shape like an inverted pyramid. Salient clinical features are blue sclerae, deafness due to otosclerosis, blue tympanum, hyper-

laxity of ligaments, occasionally brittleness of hair and nails, and abnormalities of tooth enamel. The pathology is essentially an osteoblastic deficiency of the periosteum. Transverse growth of the shaft and ossification of the membranous bones and portions of the skull are chiefly affected.

Atrophy of Disuse. In disuse atrophy[7], porosis occurs in the part or parts which are immobilized. Thus when a child is placed in a body cast, rapid demineralization is observed. Freely moving extremities are usually uninvolved. Hypercalciuria and renal calculi are fairly common.

The pathogenesis of disuse atrophy is believed to be due to the removal of the normal stress stimulation of osteoblasts. The intricate trabecular pattern of normal bone is constantly changing in accordance to Wolff's law. When the stress stimulus is absent, new osteoid tissue is not formed and disuse atrophy or osteoporosis results.

In long standing loss of mobility, such as occurs in poliomyelitis or motor nerve injuries in childhood, the affected bone becomes thin and over-modeled. The shaft appears very slender in proportion to the epiphyseal ends of the bone.

When disuse is complicated by severe pain, atrophy rapidly develops. The demineralization may assume a spotty character and is often called Sudeck's atrophy. Perhaps the sensory nerve stimulation and its reflex action on the vessels play a role.

Post-Menopausal Osteoporosis. Gardner and Pfeiffer[17] found that estrogen stimulated endosteal bone formation in pigeons. In man there is good evidence that the female sex hormone also stimulates endosteal bone formation. The lack of estrogenic substances, such as occurs in the post-menopausal state, causes in certain women clinical changes associated with osteoporosis. Shortening of stature, fractures, angulation, and kyphosis of the spine are noted. Roentgenograms reveal signs of osteoporosis in no way distinguishable from osteoporosis due to other causes.

It is believed the estrogens are necessary for the formation of organic matrix bone. The administration of high calcium phosphate diets with Vitamin D are definitely contra-indicated in all osteoporoses. The excess salts may encourage renal calculus formation.

In congenital hypoestrinism or ovarian agenesis, osteoporosis develops at puberty. The epiphyses are delayed in fusion. Changes in the spine such as rounded kyphosis and a so-called "epiphysitis" occur. The ring epiphyses are irregularly formed, giving the vertebrae a notched or wavy appearance.

Scurvy. Scurvy in infancy also has a distinctive roentgenological pattern[16]. The lack of Vitamin C interferes with collagen and matrix formation during a period of rapid growth. The osteoblasts exhibit degenerative changes and this situation is reflected in a lowering of the serum alkaline phosphatase. The ground glass appearance of the bones and epiphyses, the "penciled" white line of the cortex are quite characteristic. In addition brittleness of the bones is evidenced by infractions, spurring and metaphyseal corner defects. A zone of radiolucency can be seen in the region just below the metaphyseal plate. Frequently fractures occur through this zone and the plate together with the epiphysis is dislocated. Subperiosteal hemorrhages can be noted in more advanced cases when healing begins.

Senile Osteoporosis. Senile osteoporosis is perhaps the most common type of decreased bone density seen in radiologic practice. Degenerative changes such as osteoarthritis of the spine and calcification in the vessels are almost invariable concomitant findings. The chief difficulty encountered

by the radiologist is in trying to decide whether the changes are a part of the physiologic aging process or whether they may be clinically significant.

The osteoporosis in senility may well be due to a number of factors, such as generalized suppression of hormone secretion and the degenerative effect on cells due to the aging process. A striking example of the difficulty the aged have in producing osteoid tissue is seen when one studies the healing of fractures in elderly people.

Cushing's Syndrome or Basophilism. The radiologic findings in basophilism cannot be differentiated from the general group of osteoporosis. Clinically there are the following features: 1) peculiar fat distribution resulting in the "moon face" and "buffalo hump" with thin arms and legs, 2) hirsutism, 3) acne, 4) thin red skin with striae, 5) hypertension, 6) amenorrhea with loss of libido, 7) diabetes, 8) lymphocytopenia, 9) elevated serum sodium and bicarbonate, and 10) low serum potassium and chloride.

The cause is ascribed to the overproduction of adrenal cortical "sugar" or "S" hormone. This hormone exerts an anti-anabolic effect on osteoid production resulting in osteoporosis and cessation of skeletal growth in children. The disease may be due to a primary adrenal adenoma, hyperplasia or carcinoma. Secondarily the adrenal may be stimulated by overactivity of the basophil cells in the pituitary gland. It is probable that these basophil cells produce an excess of adrenal corticotrophic hormone (ACTH).

In Cushing's syndrome the endocrine factor probably acts primarily on the synthesis of protein which is necessary for osteoid tissue formation. The osteoporosis seen in cases of malnutrition and also in cases with the so-called "alarm reaction" may also be attributable to an aberration of protein metabolism. In severe cases of hyperthyroidism one occasionally sees a generalized osteoporosis[23] or more rarely a picture simulating malacic bone disease. The mechanism is not known. However, it may be postulated that the catabolism of protein may be the predominant factor and will be evidenced by osteoporosis, whereas, if the excretion of calcium salts predominates, there will be a pattern simulating osteomalacia.

Comparison of Malacic Bone and Porotic Bone. Radiologically the 2 main groupings of generalized decreased bone density may be differentiated into a) the group due to a defect in mineral metabolism, the malacic group, and b) the group due to a defect in the metabolism of the organic portion of bone variously called osteoid tissue or bone matrix, the porotic group.

The first due to an aberration of mineral metabolism can be exemplified in an exaggerated manner by rickets.[15] The second group due to an aberration of osteoid tissue likewise can be best exemplified by scurvy. The radiologic differences can best be appreciated by charting the findings.

Not many years ago many authorities challenged the possibility of differentiating the bony changes of scurvy and rickets. However, the modern radiologist is confident that he can discern differences between clinical cases of infantile scurvy and rickets.

Thus scurvy and rickets can be utilized as prototypes to differentiate mineral metabolic diseases, the malacic group from organic matrix diseases, the porotic group. It must be remembered that the very active metabolism, and especially the growth of the epiphyses and metaphyses in infants, exaggerate

the Roentgen changes. Since in adult bones the epiphyses have fused with the metaphyseal zone, comparable with the metabolic exchange in other portions of the bone.

DIFFERENTIAL DIAGNOSIS OF DECREASED BONE DENSITY. There are numerous bone diseases which can be confused with both malacic and porotic diseases. Certain instances of diffuse multiple myeloma[5], in which localized punched-out lesions are not present, may simulate osteoporosis and occasionally osteomalacia. The spine and pelvis may show a generalized demineralization. Even "fish" vertebrae have been noted. Usually the correct diagnosis can be established by finding increased globulin in the serum, Bence-Jones protein in the urine and plasma cells in the bone marrow. The serum calcium may be elevated as in hyperparathyroidism.

Occasionally metastatic carcinoma may be confused with generalized metabolic bone disease. Increased urinary and serum calcium have been noted. Most often a complete roentgenological study of the skeletal system will reveal the true disseminated character of the metastatic lesions. A bone biopsy usually yields definitive information.

Leukemia, the reticuloses, certain

Chart 4.

COMPARISON OF RADIOLOGIC FINDINGS

	RICKETS	SCURVY
1. General appearance of long bones	Coarse demineralization. A "fibrous effect"	Ground glass Washed out effect
2. Plasticity	Softening	Brittleness
3. Reaction to trauma and stress	Bowing Greenstick fractures Widening & cupping of metaphysis.	Infractions Dislocation of epiphyses and plate. Corner sign
4. Cortical or compact bone	Absent or diminished Subperiosteal resorption.	Thin but clear Endosteal resorption
5. Cancellous or spongy bone	Primary trabeculae, remaining secondary trabeculae resorbed. Preferential reaction to Wolff's law.	Primary and secondary resorbed. No reaction to Wolff's law.
6. Osteoid overgrowth.	Osteoid cysts (rare). Provisional zone of calcification radiolucent. Epiphyses—coarse, radiolucent but growing. No cortical edge.	None. Not formed. Do not grow. Fine, radiolucent. Edge present. Ring sign. Wimberger.
7. Subperiosteal hemorrhage	None	± present
8. Costochondral junctions	Rachitic rosary Costochondral junction	Bayonetting of ribs Infractions
9. Skull	Bossing—thin Hot cross bun, coarse	No change
10. Mandible	Coarse	Ground glass
11. Teeth and surrounding	No lamina dura	Lamina dura thin but distinct.

anemias and polyostotic fibrous dysplasia have on occasion caused confusion with metabolic bone disease. These entities can be excluded by careful consideration of blood and urine chemistries, peripheral blood and bone marrow patterns. The final arbiter may be a bone biopsy.

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PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF FEBRUARY 19, 1952

Respiratory Impairment in Emphysema and Asthma. D. V. BATES, M.R.C.P., (Medical Professorial Unit, St. Bartholomew's Hospital, London.) Respiratory function in normal subjects and in cases of emphysema and asthma has been investigated by two methods: firstly, by measuring the uneven distribution of inspired gas by means of a closed circuit technique using helium, and secondly, by determining the rate of uptake of carbon monoxide gas using an open circuit method. The first of these techniques has already been described. In the second, the rate of uptake of carbon monoxide is measured under steady state conditions, and is expressed as a percentage of the total volume of carbon monoxide inspired. The inspired gas contains 0.15% CO in air, and all gas analyses have been made on an infra red analyser. Young normal subjects have a mixing efficiency of between 60% and 95% with a mean of 75%, and were found to take up an average of 53% of inspired CO. Old normal subjects were found to have a significantly lower mixing efficiency, and a slightly lower average rate of uptake of CO though the difference between them and the young normals was not statistically significant as the groups were small in number. Forty-three cases of emphysema had an average mixing efficiency of 25%, and took up an average of 29% of inspired CO, the lowest percentage uptake found being 12% and the highest 40%. A group of young adults, below the age of 19, suffering from asthma were studied, and it was found that although in the majority of these cases the degree of mixing impairment was as severe as that found in emphysema, in only 1 case was the rate of uptake of CO significantly lower than in the normal subjects studied. It is thought that these findings indicate that although the unevenness of distribution of inspired gas may be as great in asthma as in emphysema, the two conditions differ in one important respect. In the case of emphysema there is impaired gas clearance from the well ventilated parts of the lung, whereas in asthma a normal proportion of carbon monoxide can be removed from the inspired gas, and hence the relatively well ventilated areas of the lung must be capable of normal function in this respect.

A New Method of Producing Repetitive Short Bursts of Idioventricular Rhythm in the Dog. A. SOKALCHUK, R. E. DAILEY and J. N. CROWDER (Research and Development Division, Smith, Kline and French Laboratories, Philadelphia, Pa.). Dogs are anesthetized with a thiopental-barbital mixture. Caffeine sodium benzoate, 100 mg./kg., is injected intramuscularly. The left chest is opened under interrupted positive pressure (reasonably constant source) artificial respiration. To prevent hypercapnea under the experimental conditions, respiration is maintained at a rate of 60 to 70 per minute. A critical level of hypoxia is achieved by reducing pulmonary volume exchange to the point that minimal, continuous, reflex muscular attempts at respiration are just produced. Atelectasis should be promptly corrected if it occurs. Mean arterial blood

pressure and muscular attempts at respiration are recorded. The electrocardiogram is continuously observed on a cathode-ray oscilloscope; controls and significant changes are permanently recorded. Both control and test animals are challenged every 5 to 10 minutes with selected doses of epinephrine intravenously about one hour after caffeine is given.

Myocardial irritability threshold is assigned to that dose of epinephrine that produces a definite but short burst, 5 to 10 successive beats, of idioventricular rhythm. This threshold remains reasonably constant for 2 to 3 hour periods. Anti-arrhythmic agents cause marked elevations in threshold of myocardial irritability as indicated by multiple increases in control dose of epinephrine required to elicit a threshold response.

By this method, doses of 0.5 to 5.0 mg./kg. intravenously of 'Dibenzyline' (N-(phenoxyisopropyl)-N-benzyl-β-chlorethylamine) and doses of 50 mg./kg. intravenously of procaine amide produce comparable elevation of the epinephrine induced arrhythmia threshold. The brief duration of action of procaine hydrochloride precludes an accurate determination of peak degree of activity; however, significant degrees of protection are observed in doses of 2.5 to 5.0 mg./kg. intravenously. Quinidine sulfate and 'Dilantin' (diphenylhydantoin sodium) exhibited significant degrees of protection. Diethylaminoethanol yielded no protection in the dose range studied and in one experiment lowered the threshold of myocardial irritability.

This method permits a semi-quantitative evaluation of both degree and duration of protective activity of drugs against ventricular arrhythmias.

The Central Mechanism of Emotions. E. Spiegel, H. T. Wycis, H. Freed and K. Orchinik. (Departments of Experimental Neurology, Neurosurgery and Psychiatry, Temple University School of Medicine). Based upon a study of 58 cases in which circumscribed lesions of various thalamic nuclei were produced, the authors arrive at the conclusion that it is not possible to refer emotional reactions to a single circumscribed nucleus within the diencephalon or to its connections with the frontal lobes, but that there exists a multiple representation of its function. Following the elimination of one or two of these circuits, others are able to compensate for the loss. As far as our present experience permits us to localize this function, the following systems seem to play a part: (a) the connection of the dorsomedial nuclei with the frontal association areas, (b) connections of the anterior nuclei with the cingulate gyrus, (c) connections of the hypothalamus with the frontal lobe, (d) intradiencephalic connections chiefly between the dorsomedial nuclei and the hypothalamus, perhaps also between the anterior nuclei and the mammillary bodies.

The Response of Coronary Venous Blood Oxygen Saturation to Intravenous Injection of Epinephrin and Norepinephrin. J. W. West, H. E. Lessner, M. E. Hess, P. H. Bulle, M.D., E. L. Foltz, M.D. (Departments of Pharmacology and Medicine, University of Pennsylvania). Changes in the coronary venous blood oxygen saturation were studied in normal intact dogs under the influence of morphine and combination barbiturate anesthesia (dial, urethane, pentobarbital). Arterial samples were obtained through a fem-

oral puncture, while coronary venous sampling was accomplished by catheterization of the coronary sinus under fluoroscopic control. Blood pressure was recorded by the Lilly capacitance manometer from the femoral artery. The drugs used in these series of study were the pure forms levo-epinephrine bitartrate and levo-norepinephrin bitartrate.

Following the injection of saline in our control series, there was but a slight mean change in the coronary venous blood oxygen saturation (–2%), mean arterial blood pressure (–4 mm. Hg), and cardiac rate (–2 beats/min.). In a dose-response series in which doses of 1 to 100 gamma/kilo of either drug were used, the changes in coronary venous oxygen saturation, mean arterial blood pressure and cardiac rate were similar for both drugs, but varying in degree with the dosage. The observed change in coronary venous blood saturation was of short duration and occurred with the maximum rise in blood pressure and a corresponding bradycardia. A dose of 5 gamma/kilo of either drug produced a mean rise in the coronary venous oxygen saturation of approximately 34% and a mean rise in mean arterial blood pressure of 62 mm. Hg which proved to be highly significant as statistically shown with "Students t" test.

We have observed in several experiments after atropinization, the injection of epinephrin or norepinephrin did not produce this increase in coronary venous blood oxygen saturation and the bradycardia, while still preserving the rise in mean arterial blood pressure. This observation suggests that the bradycardia is partly responsible for the favorable coronary venous oxygen exchange and that the bradycardia is due to a pressor reflex effect with the vagus nerve as the effector.

In conclusion, under the conditions of these studies, there appears to be no essential difference between the actions of epinephrin and norepinephrin on the coronary blood oxygen exchange, arterial blood pressure and cardiac rate.

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BOOK REVIEWS AND NOTICES

CLINICAL HEMATOLOGY. By MAXWELL M. WINTROBE, M.D., Ph.D., Professor of Medicine, University of Utah College of Medicine. 3d ed. Pp. 1048; 220 ills., 17 plates. Philadelphia: Lea & Febiger, 1951. Price, $12.50.

THIS is a splendid revision of a work which has earned the highest regard of specialists in the field of hematology, as well as of physicians and medical students in general. The present edition maintains the high standards of its predecessors. Among the changes which have been made are extensive revisions of the sections on bone-marrow, red cell production and destruction, coagulation, and the effects of irradiation. New sections have been added which deal with cytochemistry, splenic puncture, and the role of heredity in hemopoietic disorders. Special consideration is given to newer therapeutic agents, including vitamin B_{12}, adrenocorticotropic and adrenocortical hormones. These are only a few of the changes which led to enlargement of the text by some 180 pages.

In addition to the comprehensive clinical and technical discussions, Dr. Wintrobe has provided a selected bibliography of almost 4000 references.

It should be apparent from this all too brief review that this new edition will continue to provide an authoritative, up-to-date reference for all aspects of clinical hematology.

C. Z.

THE CLINICAL USE OF FLUID AND ELECTROLYTE. By JOHN H. BLAND, M.D., Assistant Professor of Medicine, University of Vermont College of Medicine. Pp. 259; fig. 75. Philadelphia: W. B. Saunders Co., 1952. Price, $6.50.

THIS manual presents effectively the cumulative information concerning the chemical pathophysiology encountered in a wide variety of medical and surgical conditions. Generous use is made of the Gamble-type diagrams to illustrate the fluid and electrolyte derangements seen in renal disease, congestive failure, diabetes mellitus, pediatrics, geriatrics, and many other situations. The author reserves a special plea for more sagacious therapy in the case of the aged who tolerate electrolyte shifts and dehydration poorly. As a practical guide to the diagnosis and treatment of fluid abnormalities, this book will be of great value to every physician.

C. S.

THE TEMPOROMANDIBULAR JOINT. Edited by BERNARD G. SARNAT, M.D., M.S., D.D.S., Professor and Head of the Department of Oral and Maxillofacial Surgery, College of Dentistry, University of Illinois. Pp. 144; 52 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $4.75.

The Temporomandibular Joint edited by Sarnat is a monograph in the American Lecture Series and brings together five authorities on this subject.

The purpose of the monograph is to bring the knowledge of the articulation and surrounding structures up-to-date and to disprove certain misconceptions which have been perpetuated from one report to another. The functional anatomy, histopathology, and pathology of the area are very clearly explained and illustrated and the diagnosis of such disorders is very logically correlated. Since condylar growth plays such an important role in facial development, this aspect is given clear and concise consideration. Dental occlusal factors would appear to play a sizeable role in correctable disorders, and accordingly, due emphasis is given to this phase.

R. H.

MEDICAL CLINICS OF NORTH AMERICA. Chicago Number. January, 1952. Pp. 301; 28 ills. Philadelphia: W. B. Saunders Company, 1952. Price, $15.00, a year.

THIS volume includes a symposium on "Recent Advances in Cardiovascular Diseases" (228 pages), and several clinics on other subjects (Recent Studies on ACTH and Cortisone, Practical Problems in the Use of Antibiotics, The Physician in an Atomic Attack, Advances in Infant Nutrition, and The Patient and His Physician). The chapters on the whole are excellent and worthy of careful perusal by the practitioner. A few are weak, however. We are told (page 112) that the "washing out" of the blood carbon dioxide in advanced congestive failure leads in certain patients to ACIDOSIS!!! We are told also (pages 110-111) that "some instances of hypertension are due to the extra effort put out by a failing heart," and that, on the other hand, some patients "may actually have their blood pressure driven up so high by prolonged digitalis administration as to cause rupture of a cerebral vessel." The low salt syndrome is described very poorly and nothing is said concerning therapy for cases in

which this syndrome complicates severe and persistent congestive failure. The electrocardiographic "acute phase" of cardiac infarction is said to be prolonged by dicumarol therapy, and this is apparently supposed to be a good effect. Does this mean that the "current of injury" effect of freshly damaged myocardium is prolonged and that this is desirable? The chapter on the pathogenesis and treatment of hypertension contains a paragraph entitled "Drugs of Proved Usefulness" which is a classic of non-committal writing.

T. D.

BRAIN TUMORS OF CHILDHOOD. By HENRY M. CUNEO, M.D., Assistant Clinical Professor of Neurosurgery, and CARL W. RAND, M.D., Clinical Professor of Neurosurgery, University of Southern California. Pp. 224; 61 ills. Springfield, Illinois: Charles C Thomas, 1952. Price, $5.75.

THIS monograph presents the authors' experience with 83 verified brain tumors of childhood. The first 12 chapters are each devoted to a specific tumor group. The beginning of each chapter contains historical references followed by a statistical analysis of the authors' cases, Roentgen-ray findings, survival period and final comment. The last chapter considers general symptomatology, differential diagnosis and diagnostic aids. The illustrations of the gross lesions are helpful and are complimented by excellent photomicrographs. This compact little book will be welcomed by all interested in the problems of brain lesions in children.

M. S.

A MANUAL OF PARASITOLOGY FOR MEDICAL STUDENTS AND BEGINNERS. By MARK M. SCHAPIRO, M.D., M.S., Fellow, Royal Society of Tropical Medicine and Hygiene. London; Fellow, International College of Surgeons; Formerly Instructor, Department of Bacteriology and Lecturer in Parasitology, Stritch School of Medicine, Loyola University; Consultant in Tropical Medicine and Parasitology, American Hospital, Chicago, Illinois. Pp. 140; 8 ills. New York: Grune & Stratton, Inc., 1951. Price, $5.50.

THIS manual has an unusual format. The textual material is arranged in double columns on a 6″ x 8¾″ page. The illustrations consist of 8 plates and a colored frontispiece.

The author, as indicated in his preface, has limited the presentation of the subject to a brief discussion of general principles and the biological differentiation of the more important parasites of man, including a chapter on laboratory diagnostic methods.

Since this text is primarily designed for the medical student, many may regret that greater emphasis has not been placed on epidemiology and pathogenesis.

Two typographical errors were noted (page 15—I. butschlii; page 65—H. heterophyes).

The inclusion of a brief section on Arthropods would be of value.

E. S.
A. L.

SURGERY OF PERIPHERAL NERVES. By EMIL SELETZ, M.D., F.A.C.S., F.I.C.S. Asst. Clin. Prof. Neurolog. Surg. Univ. of South. California Sch. of Med. Pp. 181; 136 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $10.75.

THE author has written a well-illustrated book. It is particularly useful for a practicing neurosurgeon. In the surgical attack on peripheral nerve injuries, a number of new incisions are introduced, which are designed for good exposure as well as preventing restrictive scars. The study of each major nerve is simply outlined; the author presents the essential anatomy, the surgical anatomy, the course and distribution of the blood vessels, the level of the lesion, characteristic symptoms, the incisions for surgical exploration, and the operative procedures. The chapter on the hand is particularly clear and useful in understanding the mechanics of finger movements with reference to the lesions of the median, ulnar, and radial nerves. These mechanics are beautifully illustrated with excellent photographs. A similar study has been presented for the mechanical movements of the toes and foot.

This book serves as an excellent reference for special neurosurgical problems with respect to the surgery of the peripheral nerves.

H. W.

OPHTHALMOLOGY. By ARNO E. TOWN, Prof. of Ophthalmol., Jefferson Med. Coll., Phila. Pp. 511; 208 ills.; 4 plates in color. Phila.: Lea & Febiger, 1951. Price, $10.00.

THIS book is written by a group of outstanding ophthalmologists in an effort to provide a suitable treatise for the undergraduate student and general practitioner. It would seem that it is admirably suited as an introductory text for the beginning resident in ophthalmology but it is too detailed to hold the interest of the average physician.

The textual material is treated in the usual way by considering the separate anatomic parts and the diseases affecting each. Although this approach has merit, the practical application of the facts is not met with in

this way, and what is really required is a clinical treatise which treats the situation as it is presented in the patient. The author made a brief attempt at this in Chapter 19 on Symptomatic Diagnosis. This chapter, however, could stand considerable improvement and amplification. For example, the author makes the statement, "If the patient suffers excruciating pain with a sudden loss of vision, the diagnosis is undoubtedly acute glaucoma." This kind of statement obviously accomplishes no good purpose in increasing the clinical acumen of the general practitioner.

This book is highly recommended to the junior resident in ophthalmology. W. H.

NEWER ETHICAL PROBLEMS IN MEDICINE AND SURGERY. By BERNARD J. FICARRA, M.D., K.S.G. Pp. 168. Westminster, Md.: The Newman Press, 1951. Price, $3.75.

THIS book contains a discussion of such ethical and sociological problems as abortion, ectopic gestation, mutilation (including the moral implications of lobotomy), sterilization, improper use of drugs, contraception, euthanasia, artificial insemination, socialized medicine, autopsies, and compensation medicine. A chapter on the moral aspect of professional conduct presents the principles of medical ethics published by the American Medical Association. These are reproduced in toto. The chapter on socialized medicine summarizes briefly the menace of governmental domination of medical practice and reproduces the program of the American Medical Association for the advancement of Medicine and Public Health. The special dictates of the Catholic Church will be found in the chapters on sterilization and contraception. T. D.

DR. SPITZER'S ARCHITECTURE OF NORMAL AND MALFORMED HEARTS. A PHYLOGENETIC THEORY OF THEIR DEVELOPMENT. With a summary and analysis of the theory by MAURICE LEV, M.D., Assoc. Prof. of Pathol., Univ. of Illinois, and ALOYSIUS VASS, M.D., Consultant Pathologist, Veterans Admin. Hosp., Poplar Bluff, Missouri. Pp. 145; 30 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $5.00.

SPITZER first presented his phylogenetic theory of the development of the normal mammalian heart in 1919 and 1921. Later (1923) he applied this theory to transposition complexes. Following criticism of the theory, it was re-explained and extended by the author on several occasions. Basically the theory relates the definitive architecture of the mammalian heart to phylogenetic forces operating by hydrodynamic means and catalyzed by the development of pulmonary respiration. This important hypothesis and the arguments supporting it have not been sufficiently available to the American physician because they were written in difficult German. Drs. Lev and Vass have circumvented this by providing an excellent translation. Furthermore since Spitzer's approach contains many faults, and in some respects does not conform to later embryological research, the translators have added a summary and analysis of the theory with a criticism and a modification. The book is to be highly recommended to all who are interested in the embryology of the heart and to those clinicians who are interested in congenital heart disease. T. D.

PLASTIC SURGERY OF THE NOSE. By JAMES BARRETT BROWN, M.D., Prof. of Clin. Surg., Washington Univ. Sch. of Med., and FRANK MCDOWELL, M.D., Asst. Prof. of Clin. Surg., Washington Univ. Sch. of Med. Pp. 427, 379 ills., 48 in color. St. Louis: C. V. Mosby, 1951. Price, $15.00.

THE above-mentioned volume is a most valuable text which is hard to describe adequately in a Reviewer's paragraph. For the surgeon with experience, or the beginner looking for help, this book fills a long-felt need. Herein are related operative techniques proved by experience and illustrated in an adequate "how to do it" manner. For the internist or the practitioner of general medicine the portion on indications is important. The demand for rhinoplasty is increasing. If a nasal deformity exists, this procedure should be recommended because what may be completely accepted by one patient may be distressing to another. This book is highly recommended to all concerned. D. M.

TEXTBOOK OF REFRACTION. By EDWIN FORBES TAIT, M.D., Ph.D., Assoc. Prof. of Ophthalmol., Temple Univ., Phila. Pp. 418; 93 ills. Phila.: W. B. Saunders Co., 1951. Price, $8.00.

THIS book is designed primarily for the student group preparing for practice in the field of eye work. The early chapters discuss basic material and concepts which the author considers necessary for the study of refractive errors and oculomotor anomalies.

A thorough understanding of such basic equipment as the trial frame, trial case, action and properties of lenses, prisms and cycloplegics is most important to the student. Chapter 28 presents a helpful correlation. The index is good. I. T

BIOLOGICAL ANTAGONISM. THE THEORY OF BIOLOGICAL RELATIVITY. By GUSTAV J. MARTIN, Research Director, National Drug Co. Pp. 516, 64 ills. Phila.: Blakiston Co., 1951. Price, $8.50.

THIS book represents a current summary of knowledge in the field of displacement. The concept of metabolite analogues is well presented. Chapters representing enzymatic inhibition, pharmacologic aspects, p-aminobenzoic acid, sulfonamides, folic acid, amino acid analogues, proteins and protein antagonisms are included. Discussions of metabolite analogues of pantothenic acid, pteroylglutamic acid, thiamine and riboflavin, pyroxidine, nicotinic acid and biotin, choline, inositol, and B_{12} are especially valuable. Other sections are equally well done. The importance of "growth factors" as "essential metabolites which can not be synthesized" is stressed. This work is useful to those interested in chemotherapy which should include pharmacologists, immunologists, bio-chemists, and bacteriologists.

M. O.

NEW BOOKS

Renal Function. Transactions of the Second Conference, October 19-20, 1950, New York, N. Y., Sponsored by the Josiah Macy, Jr. Foundation. Edited by STANLEY E. BRADLEY, M.D. Pp. 178; 27 ills. New York: Josiah Macy, Jr. Foundation, 1951. Price, $3.00.

PHYSICIANS interested in basic phenomena related to renal function will be as delighted with this volume as they were with that which reported the first conference. The transactions have been faithfully transcribed and the informality of the discussions carried over to the printed page, thus permitting the reader to share in the "give-and-take" inherent in this type of meeting. The topics discussed were: Adrenal Cortical Hormone and Related Hormones in Water Metabolism, Antidiuretic Factors, Some Pituitary and Adrenal Influences on Renal Function in Man, The Excretion of Sodium in Relation to Glomerular Filtrations, Endocrine Factors in the Utilization of Glutathione, and Bioassay of Sodium-Retaining Corticoids and Some Changes in Excretion of these Substances in Disease. The Foundation is to be congratulated for having made available in one well-edited volume all this up-to-date and valuable material on an extremely important subject.

T. D.

Adrenal Cortex. Transactions of the Second Conference, November 16-17, 1950. Edited by ELAINE P. RALLI, M.D. Pp. 209; 68 ills. New York: Josiah Macy, Jr. Foundation, 1951. Price, $3.00.

THE topics presented and discussed by the group of leaders in adrenal cortex research who participated in this conference include: The Present Status of the Chemistry of ACTH, Regulation of Pituitary Adrenocorticotropic Activity, The Relation of the Adrenal Hormones to the Hypersensitive State, Hyaluronidase and the Adrenal Cortical Hormones, and Further Clinical Studies with ACTH and Adrenal Cortical Hormones. This volume is highly recommended to all physicians to aid them in keeping abreast of the advancing tide of adrenal cortex knowledge and its manifold practical applications.

T. D.

Nerve Impulse, Second Conference. By DAVID NACHMANSOHN, M.D., Editor. Pp. 204; 37 ills. Caldwell, N. J.: Progress Associates, Inc., 1951. Sponsored by Josiah Macy, Jr. Foundation, New York, N. Y. Price, $3.50.

THIS second conference on nerve impulse discusses ionic problems, excitability, central excitation and inhibition, anesthetizing action and metabolism. All twenty-five participants in this group are authorities in their respective fields. The informal character of the book has been preserved. Bibliographies and illustrations are valuable. Current concepts on the topics considered are well presented. Discussions are fully set out. Newest concepts and techniques are presented in such a manner as to be useful to physician, investigator, teacher and student. This book is a most pertinent one in its field.

M. O.

Medical Milestones. By HENRY J. L. MARRIOTT, M.D., Assistant Professor of Medicine, University of Maryland, Pp. 293; 6 ills. Baltimore: Williams and Wilkins Co., 1952. Price, $3.50.

THE present day insatiable public demand for popular articles dealing with medical progress has led to the appearance of many accounts in which the enthusiasm of the author has carried him far beyond the realms of scientific reality and harm has been done in many instances. It is a great pleasure therefore to read a volume such as this one in which a physician, blessed with exceptional literary ability, has presented for the nonmedical public a completely accurate summary of many outstanding recent medical triumphs. The material is presented in a non-technical fashion and in a very readable style. It is a book to be highly recommended for public consumption.

T. D.

Factors Regulating Blood Pressure. Transactions of the Fifth Conference, February 15-16, 1951. Edited by BENJAMIN W. ZWEIFACH, M.D., and EPHRAIM SHORR, M.D. Pp. 238; 49 ills. New York: Josiah Macy, Jr. Foundation, 1951. Price, $3.75.

REPORTING the fifth and final Conference on Factors Regulating Blood Pressure, this volume deals mainly with arteriosclerosis. As with the previous representatives of this series, the discussions following the presentation are invaluable to the reader in weighing the opinions of the participants who represent a variety of approaches. The following topics are discussed: Chemical

Studies of the Blood in Arteriosclerosis; Blood Lipids in Experimental Arteriosclerosis; Lipoproteins and Atherosclerosis; The Regulation of Fat Deposition by the Lipfanogens and Antilipfanogen; Experimental Hypertension; Incidence of Atherosclerotic Disease During War Years; Cardiovascular Disease in Ceylon; Blood Flow, Blood Pressure and Intimal Thickness as Factors in Localizing Atheroma Formation; Changes in the Media in Human Arteriosclerosis; Studies on Experimental Atherosclerosis and Hypertension; and the Effect of Experimental Renal Hypertension on Experimental Cholesterol Atherosclerosis. The reader of this volume will thus be provided with an up-to-date survey in very readable form of the progress being made in understanding the etiology of America's major public health problem.

T. D.

NEW EDITIONS

Internal Medicine, Its Theory and Practice. Originally edited by JOHN H. MUSSER, M.D., F.A.C.P., Late Professor of Medicine, Tulane University of Louisiana. 5th Ed. Edited by Michael G. Wohl, M.D., F.A.C.P., Assoc. Prof. of Med., Temple Univ. Sch. of Med. Pp. 1563; 236 ills.; 10 plates. Philadelphia: Lea & Febiger, 1951. Price, $15.00.

THE aim of the new editor of the well-known Musser textbook of medicine to present in one volume a comprehensive survey of the entire field of internal medicine has been achieved in an admirable fashion. The 81 contributors have been well chosen and the arrangement and editing have been done in such a fashion as to provide excellent uniformity. Special features of this edition are the chapters on genetics, geriatrics, rehabilitation, and psychosomatic medicine and a section on the general adaptation syndrome. These contribute to the understanding of the modern conception of the "whole" patient. The book is arranged in 7 sections. The first deals with infectious disease; the second, with diseases due to physical and chemical agents; the third, with diseases of nutrition, metabolism, and the endocrine glands; the fourth, with diseases of allergy and collagen diseases; the fifth with systemic diseases; the sixth, with geriatrics and rehabilitation; and the seventh, with diseases of the nervous system. The illustrations have been well chosen and well reproduced and the color plates are excellent.

This is an exceptionally fine textbook of medicine and one which can be highly recommended to the student of medicine and to the practitioner.

T. D.

A Course in Practical Therapeutics. By M. D. REHFUSS, M.D., F.A.C.P., Prof. Clin. Med., F. K. ALBRECHT, and A. H. PRICE, M.D., Assoc. Prof. Med., Jefferson Medical College. 2nd Edition. Pp. 938; 96 ills. Baltimore: Williams & Wilkins, 1951. Price, $15.00.

THE second edition of this book continues to be very valuable. New drugs which have appeared since the previous edition are included. The visual system has been used effectively throughout. Treatment of symptoms and diseases is considered systematically and the arrangement has not been changed. The first section of the book deals with general therapeutic principles. The second section deals with differential diagnosis and symptomatic management. The next section gives the treatment of specific disorders except those of the nervous system. The last section concerns itself with special techniques and their application to general practice. The general practitioner will find this book very useful.

M. O.

The Surgical Practice of the Lahey Clinic. By MEMBERS OF THE LAHEY STAFF. Pp. 1014; 784 ills. on 509 figs. Philadelphia: W. B. Saunders, 1951. Price, $15.00.

THE second edition of this book will be read with interest by many surgeons. It is in no sense a textbook of surgery and it is not meant to be one. It is a book which deals almost in its entirety with the clinical surgery and techniques carried out in one of the world's leading surgical clinics. It is a well-written volume which avoids superfluous detail and assumes that the reader is a surgeon of some experience. Dr. Lahey states in the foreword his strong leanings toward standardization of surgical treatment. This is carried into this volume to a degree which at times detracts from its value in that other valuable methods of surgical treatment are not mentioned. The type and illustrations are excellent and the book definitely deserves a place in the library of all general surgeons.

H. C.

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